

Advances in
**HETEROCYCLIC
CHEMISTRY**

Edited by

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2,3-Dihydro-1,4-diazepines

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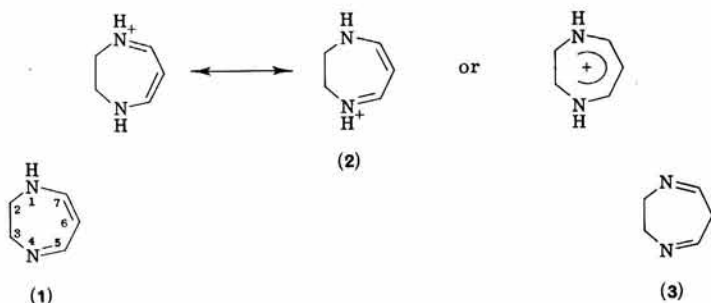
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I. Introduction

Diazepines were reviewed in a previous volume in this series in 1967,¹ in a chapter which dealt with the whole range of diazepines. The present chapter and the succeeding one in this volume deal with two particular classes of diazepines, the 2,3-dihydro- and 2,3-benzo-1,4-diazepines. The literature is covered to the end of 1972, with some later references.

The first example of a 2,3-dihydro-1,4-diazepine was prepared in 1940,² although a compound had been described³ previously as a dihydrodiazepine but, from its melting point, now appears to have been an alternative acyclic product. In recent years their chemistry has been studied extensively, particularly because of their chemical resemblance to benzenoid compounds and their quasi-aromatic⁴ or mendeic^{5,6} character. Throughout this chapter the terms "dihydrodiazepine" and "dihydrodiazepinium" are used solely to refer to 2,3-dihydro-1,4-diazepines (1) and their mono-cations (2), respectively. Spectroscopic data show that dihydrodiazepines



normally exist in the conjugated form (1) rather than in the tautomeric bisimino form (3).

II. Preparation of Dihydrodiazepines

The first diazepine to be prepared, namely the 5,7-dimethyl derivative, was obtained by condensation of acetylacetone with ethylenediamine,²

¹ F. D. Popp and A. C. Noble, *Advan. Heterocycl. Chem.* **8**, 21 (1967).

² G. Schwarzenbach and K. Lütz, *Helv. Chim. Acta* **23**, 1139 (1940).

³ M. A. Rosanova, *J. Russ. Phys. Chem.* **47**, 611 (1915).

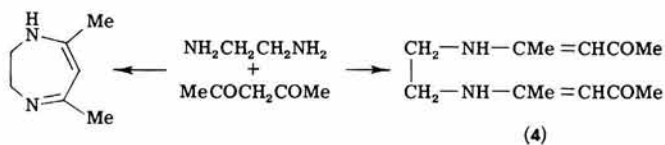
⁴ D. Lloyd and D. R. Marshall, *Chem. Ind. (London)*, 1760 (1964).

⁵ D. Lloyd and D. R. Marshall, in "Aromaticity, Pseudo-aromaticity, Anti-aromaticity" (E. D. Bergmann and B. Pullman, eds.), p. 85. Israel Acad. Sci. Humanities, Jerusalem, 1971.

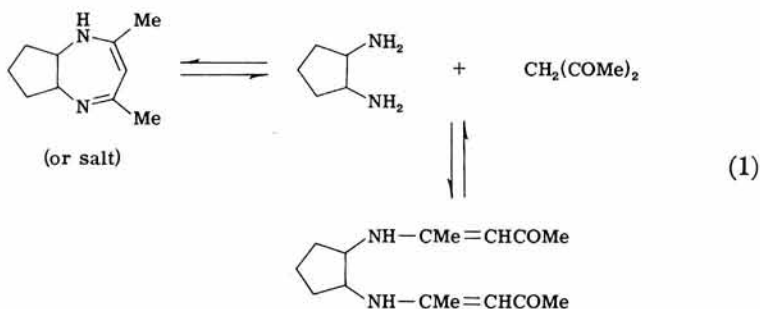
⁶ D. Lloyd and D. R. Marshall, *Angew. Chem.* **84**, 447 (1972); *Angew. Chem. Int. Ed. Engl.* **11**, 404 (1972).

and the reaction between β -dicarbonyl compounds and 1,2-diamines has remained the commonest method for the preparation of these compounds.

The original workers² had shown that under different conditions an alternative product, the bisoxoenamine **4**, was formed. Indeed some earlier workers⁷ had described the formation of only the bisoxoenamine from these reactants, while other workers³ had reported the preparation of the diazepine but quoted physical constants which are those of the bisoxoenamine. The structures of these alternative open-chain products, e.g., **4**, as bisoxoenamines rather than as tautomeric diimines, was later confirmed by NMR spectroscopy.^{8,9} A detailed examination of the reactions



between acetylacetone and *trans*-1,2-diaminocyclopentane in aqueous solution¹⁰ showed that at room temperature a bisoxoenamine was the major product in neutral and mildly alkaline conditions, whereas the dihydrodiazepine (or its salt) was the sole product at pH values less than 6 or greater than 10. The results are dependent on the (simplified) equilibria shown in Eq. (1). Dihydrodiazepines are extremely stable



compounds over a very wide range of pH and their hydrolysis may be ignored save at high alkalinity. Bisoxoenamines, on the other hand, are readily hydrolyzed and at all but moderately alkaline pH the hydrolysis

⁷ A. Combes, *C. R. Acad. Sci.* **108**, 1252 (1889); A. Combes and C. Combes, *Bull. Soc. Chim. Fr.* **7**, 788 (1892); L. Rügheimer, *Ber.* **47**, 2759 (1914).

⁸ H. A. Staab and F. Vögtle, *Chem. Ber.* **98**, 2681 (1965).

⁹ D. Lloyd, R. H. McDougall, and D. R. Marshall, *J. Chem. Soc. C*, 780 (1966).

equilibrium is such that this condensation is effectively suppressed, leaving formation of the dihydrodiazepine to proceed without competition. At moderately alkaline pH, however, the bisoxoenamine is stable and furthermore precipitates from solution. Thus its formation competes successfully with the alternative reaction and it is the predominant product. At higher temperatures the yields of bisoxoenamine drop sharply even at the most favored pH values.¹⁰ Almost identical results were found in reactions of other alicyclic or aliphatic diamines with acetylacetone.¹¹

In general the preferred method of preparation for most bisoxoenamines is by mixing the reactants in methanol or ethanol at room temperature,⁹ while dihydrodiazepines are normally best obtained by heating the reactants in acetic acid followed by addition either of perchloric acid to precipitate the dihydrodiazepinium perchlorate or of potassium hydroxide to precipitate the dihydrodiazepine base.⁹

Sometimes slight variations in these conditions result in improved yields for individual dihydrodiazepines.¹² In particular, when aryl diketones are used as reactants, somewhat different reaction conditions may be required.^{13,14} Thus in the reaction of benzoylacetone with ethylenediamine a bisoxoenamine is the main product over a much wider pH range, while in alkaline solution yet another product was formed, namely the bisimine derived from ethylenediamine and acetophenone, this ketone resulting from hydrolytic cleavage of the diketone.¹³ Amended conditions were thus required to obtain the best yields of dihydrodiazepine in this case¹³ and also from other aryl diketones,¹⁴ the differences being due to the lower reactivities of aryl-substituted carbonyl groups.

Dihydrodiazepinium salts can also be prepared by the reaction of *N*-alkyl,¹⁴ *N*,*N'*-dialkyl,^{12,14,15} or *N*,*N'*-diarylethylenediamines^{15,16} with β -dialdehydes or β -diketones. When both the diamine and dicarbonyl compounds used are unsymmetric, two isomeric dihydrodiazepines may be obtained; thus, for example, *N*-methylethylenediamine and benzoylacetone give a mixture of 1,5-dimethyl-7-phenyl- and 1,7-dimethyl-5-phenyldiazepines.¹⁴ The acid salt of the bis(*N*-methylanil) of malondialdehyde also reacts with *N*,*N'*-dimethylethylenediamine to give a

¹⁰ D. Lloyd and D. R. Marshall, *J. Chem. Soc.*, 2597 (1956).

¹¹ A. M. Gorrings, D. Lloyd, and D. R. Marshall, unpublished results.

¹² C. Barnett, D. Lloyd, and D. R. Marshall, *J. Chem. Soc. B*, 1536 (1968).

¹³ A. M. Gorrings, D. Lloyd, and D. R. Marshall, *J. Chem. Soc. C*, 2340 (1967).

¹⁴ A. M. Gorrings, D. Lloyd, and D. R. Marshall, *J. Chem. Soc. C*, 1081 (1969).

¹⁵ C. Barnett, H. P. Cleghorn, G. E. Cross, D. Lloyd, and D. R. Marshall, *J. Chem. Soc. C*, 93 (1966).

¹⁶ B. Eistert and F. Haupter, *Chem. Ber.* **93**, 264 (1960).

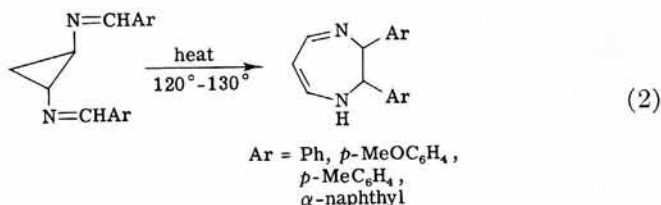
dihydrodiazepinium salt,^{16a} while the parent dihydrodiazepinium cation may best be prepared by the reaction of the bisanil or, preferably, the bis(*N*-phenylanil) of malondialdehyde with ethylenediamine.^{16b}

When condensation of acetylacetone with *C, C'*-tetramethylethylenediamine was attempted, the only product isolated, in high yield, was the acetylacetonate salt of the diamine.⁸

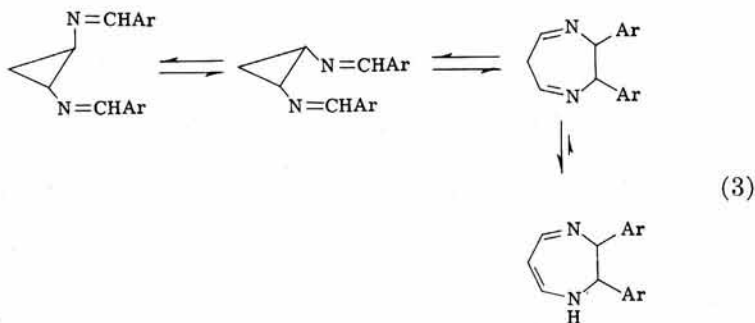
Dihydrodiazepines have also been prepared by methods not involving the use of condensation reactions.

In the first of these methods, the addition of ethylenediamine to buta-1,3-diyne gave a high yield of 5-methyldihydrodiazepine.¹⁷

In the second method the bisanils of 1,2-diaminocyclopropanes were shown to undergo a Cope rearrangement when heated, forming thereby 2,3-diaryldihydrodiazepines,¹⁸⁻²⁰ e.g., as in Eq. (2).



The reaction sequence in Eq. (3) was proposed.²⁰ It was further suggested



that the overall equilibrium is controlled by the equilibrium of the last

^{16a} G. Scheibe, J. Heiss, and K. Feldmann, *Angew. Chem.* **77**, 545 (1965); *Angew. Chem. Int. Ed. Engl.* **4**, 525 (1965).

^{16b} D. Lloyd, H. McNab and D. R. Marshall, *Synthesis*, 791 (1973).

¹⁷ W. W. Paudler and A. G. Zellar, *J. Org. Chem.* **34**, 999 (1969).

¹⁸ H. A. Staab and F. Vögtle, *Tetrahedron Lett.* 51 (1965).

¹⁹ H. A. Staab and F. Vögtle, *Chem. Ber.* **98**, 2691 (1965).

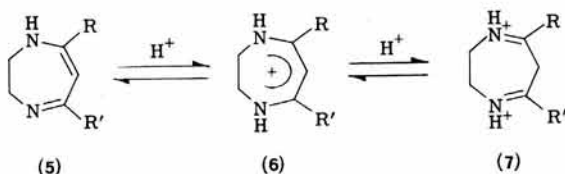
²⁰ H. A. Staab and F. Vögtle, *Chem. Ber.* **98**, 2701 (1965).

step, which is shown by all work on dihydrodiazepines to be almost entirely on the side of the conjugated form. In support of this it was shown²⁰ that the bisanil of *trans*-2,3-diamino-1,1-diphenylcyclopropane does not rearrange thermally to a dihydrodiazepine. In this case the last step is prevented by the presence of two phenyl groups at the 6-position.

1-Methyl-2-oxodihydrodiazepines have been obtained by dehydrogenation of 2,3,6,7-tetrahydrodiazepines with benzoyl peroxide and *N*-bromosuccinimide.^{20a}

III. General Stability of Dihydrodiazepines

The dihydrodiazepinium monocations (6) are extremely stable. This is



demonstrated by the enormous pH range over which the monocation is the predominant species. The pK_a values for the equilibria with the related bases (5) are about 13–14,^{9,21} while spectra of solutions indicate the absence of any notable contribution of the dications (7) in 40% sulfuric acid; only in >70% sulfuric acid do these dications predominate over the monocations.^{9,11}

The base strength of the dihydrodiazepines (5) is further shown by the fact that when they are kept in solution in chloroform for some hours they are converted into the corresponding dihydrodiazepinium chlorides, presumably by bringing about elimination of hydrogen chloride from the solvent.⁹

The stability of the dihydrodiazepines and, even more, of the dihydrodiazepinium salts, is due to their delocalized systems of π -electrons; this is especially marked in the monocations where the system is symmetrical. Calculations based on pK data suggest a resonance energy of about 19 kcal mole⁻¹ for these cations.²² A similar calculation suggests that dihydrodiazepine bases have 8 kcal mole⁻¹ less resonance energy than the cor-

^{20a} C. M. Hoffmann and S. R. Safir, *J. Med. Chem.* **12**, 914 (1969); *Chem. Abstr.* **71**, 79386 (1969).

²¹ G. Schwarzenbach and K. Lütz, *Helv. Chim. Acta* **23**, 1162 (1940).

²² D. Lloyd and D. R. Marshall, *Chem. Ind. (London)*, 335 (1972).

responding cations (in accord with the asymmetry of the conjugated system in the bases). This, however, still leaves a resonance energy of perhaps 10–12 kcal mole⁻¹ for the conjugated base structure **1**, accounting for the preference of this structure over the nonconjugated bisimine structure (**3**).

This stability is also reflected in their chemical behavior. The electronic system resists breakdown and, to use Armit and Robinson's classic phrase,²³ shows a great tendency to retain the type. This is particularly reflected in the way that these compounds undergo substitution rather than additive or destructive reactions and is discussed further in Section VIII.

Attempts have been made to dehydrogenate dihydrodiazepines or their salts using a variety of methods, but the dihydrodiazepines (or their salts) were recovered unchanged.^{9,24}

Solutions containing only the dihydrodiazepinium monocations (**6**) are unaffected by aqueous permanganate, even after several days, but solutions in either strong acid or alkali, which contain appreciable concentrations of, respectively, the dications or free bases, decolorize permanganate solutions fairly rapidly.

Catalytic reduction of a dihydrodiazepine over a prerduced platinum oxide catalyst in aqueous acetic acid has been reported.¹⁷

N,N'-Unsubstituted dihydrodiazepines and their salts resist hydrolytic cleavage over a wide range of pH values and are normally only hydrolyzed at very high or very low pH.¹⁰ With aqueous sodium hydroxide and benzoyl chloride cleavage ensues and dibenzoylethylenediamine is formed.⁹ The presence of a substituent group at the 6-position seems to make hydrolysis take place more easily. For example, 6-methyl-substituted dihydrodiazepinium salts are slowly hydrolyzed when kept in dilute sulfuric acid for some days²⁵ and 6-bromo-substituted salts are hydrolyzed quite readily under the same conditions.^{26,27} Similarly, it is not possible to isolate the base forms of 6-nitro- and 6-aminodihydrodiazepines from the respective dihydrodiazepinium cations which are, however, themselves resistant to hydrolysis in the absence of alkali.²⁸

N,N'-Disubstituted dihydrodiazepinium salts are stable in acid but decompose in alkali.^{15,16} In this case it is not possible to obtain any corresponding dihydrodiazepine bases and the only available course of

²³ J. W. Armit and R. Robinson, *J. Chem. Soc.* **127**, 1604 (1925).

²⁴ S. Veibel and J. I. Nielsen, *Mat. Fys. Medd. Dan. Vid. Selsk.* **35**, No. 6 (1966).

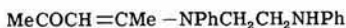
²⁵ A. R. Butler, D. Lloyd, and D. R. Marshall, *J. Chem. Soc. B*, 795 (1971).

²⁶ D. Lloyd and D. R. Marshall, *J. Chem. Soc.*, 118 (1958).

²⁷ C. Barnett, D. Lloyd, D. R. Marshall and L. A. Mulligan, *J. Chem. Soc. B*, 1529 (1971).

²⁸ A. M. Gorringe, D. Lloyd, and D. R. Marshall, *J. Chem. Soc. C*, 617 (1970).

reaction with alkali inevitably entails ring-opening. Usually the *N,N'*-disubstituted amines are the isolated products, but when 5,7-dimethyl-1,4-diphenyldihydrodiazepinium perchlorate was heated for a short time in aqueous sodium hydroxide the monooxoenamamine (8) was isolated.¹⁴

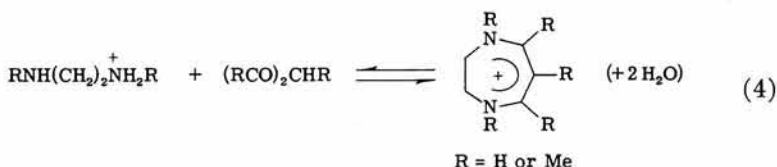


(8)

This is the only example of the isolation of this type of product from hydrolysis of a dihydrodiazepine.

IV. Stability Constants of Dihydrodiazepines and Hydrolysis Equilibria

The marked chemical stability of dihydrodiazepines and their ready formation in aqueous solution are reflected in the stability constants for their formation. These were measured¹² for a range of methyl-substituted diazepines and referred to the equilibrium of Eq. (4).



The equilibrium constants for 25°C, ignoring the water formed, are tabulated in approximate order of stability in Table I.

When few methyl groups are present, stability is high, with values exceeding 10^9 . (Inclusion of water concentration would raise this to 10^{13} .) The 5,7-dimethyl compound, on which much experimental work has been based, is not in fact the most stable. The most striking values, however, are those for the highly substituted compounds. The last two compounds listed have never been isolated and are formed in no more than very small amounts even at the most favorable pH values. Their stability constants are very rough values based only on observed UV absorption spectra. Clearly this ring system is made less stable by crowding of substituents. This is presumably caused by distortion of the ring, though this simple explanation is not wholly satisfactory; it is not clear, for example, why (ix) should be so much less stable than (vii) or (viii).

The parent compound (I) is very difficult to prepare by the standard method from malondialdehyde and ethylenediamine,¹² although it is one

TABLE I
STABILITY CONSTANTS OF DIHYDRODIAZEPINIUM CATIONS

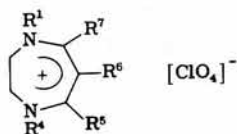
Compound No.	Methyl substituent positions					K
	4	5	6	7	1	
(i)	—	—	—	—	—	2.5×10^9
(ii)	Me	—	—	—	Me	3.2×10^9
(iii)	Me	—	Me	—	Me	7×10^8
(iv)	—	—	Me	—	—	1.3×10^6
(v)	—	Me	—	Me	—	3.4×10^6
(vi)	Me	Me	—	Me	Me	1.5×10^4
(vii)	—	Me	Me	Me	—	$\leq 10^5$
(viii)	—	Me	Me	—	—	1.0×10^3
(ix)	Me	Me	Me	—	Me	$\sim 10^{-3}$?
(x)	Me	Me	Me	Me	Me	$\sim 10^{-5}$?

of the most stable, but can be prepared readily from anils of malondialdehyde and ethylenediamine in non-aqueous conditions.^{16b} This is apparently because it is hydrolyzed relatively quickly under conditions which favor equilibrium instability. (Thus chromatographic separations, successful with most dihydrodiazepines, can result in progressive loss of material.) In contrast, derivatives substituted at positions 5 and 7 are hydrolyzed very slowly, nucleophilic attack at these positions being inhibited.

V. Theoretical Considerations

A. MODEL

A Hückel molecular orbital (HMO) model has been used to explain some of the characteristic properties of dihydrodiazepines.²⁹ The authors assumed that there was conjugative interaction between positions 4, 5, 6, 7, and 1 on the dihydrodiazepine ring but no N, N' lone pair interaction. The results obtained by this model are given in Table II.



(9)

²⁹ H. P. Cleghorn, J. E. Gaskin and D. Lloyd, *Rev. Latinoamer. Quim.* **2**, 103 (1971).

TABLE II

HMO DATA AND WAVENUMBERS FOR LONG-WAVELENGTH TRANSITIONS OF SOME DIHYDRODIAZEPINIUM PERCHLORATES, AND CHEMICAL SHIFT PARAMETERS

Salt	R ⁴	R ⁵	R ⁶	R ⁷	R ¹	$-\Delta m^a$	$\bar{\nu}$ (cm ⁻¹)	δ_H^b	ρc^a
(9a)	H	Me	H	Me	H	1.24	30960	4.9	1.120
(9b)	H	Me	H	Ph	H	1.065	29290	4.5	1.110
(9c)	H	Ph	H	Ph	H	0.94	27930	4.05	1.096
(9d)	Ph	H	H	H	Ph	0.975	26320	4.25	1.098
(9e)	Ph	Me	H	Me	Ph	0.995	28820	4.25	1.112
(9f)	H	H	H	H	H	1.275	30300	—	—
(9g)	Me	H	H	H	Me	1.17	29400	—	—
(9h)	Me	H	Me	H	Me	1.095	27730	—	—
(9i)	Me	Me	H	Me	Me	1.16	29580	—	—
(9j)	Me	Me	Me	Me	Me	1.08	27780	—	—

^a For explanation of terms, see text.

^b δ_H measured in trifluoroacetic acid.

In calculating HMO data, β_{CN} (resonance integral) is taken to be $0.84\beta_{CC}$ instead of $1.076\beta_{CC}$ as stated in Cleghorn *et al.*²⁹

B. ABSORPTION SPECTRA

Dihydrodiazepinium salts are characterized by intense absorption bands ($\epsilon = 15,000$ – $25,000$) lying between 300 and 360 nm.^{9,13–15} These high absorption values are indicative of π – π^* transitions, and this is substantiated in some cases by the presence of n – π^* transitions on their long-wavelength side.^{30,31}

The relationship between the wavenumbers ($\bar{\nu}$) of these transitions and Δm , the difference between the parameters of the lowest unoccupied MO, m_{m+1} , and the highest filled MO, m_m , have been tested.²⁹ A plot of $\bar{\nu}$ against Δm for some ten dihydrodiazepinium perchlorates illustrates the essential distinction in compound type between these salts depending on whether there are exocyclic phenyl groups or methyl groups at position 5(7), presumably because of conjugative interaction in the case of the 5(7)-phenyl substituents.

The same authors also investigated the use of the semiempirical equation

³⁰ E. Daltrozzo and K. Feldmann, *Ber. Bunsenges. Phys. Chem.* **72**, 1140 (1968).

³¹ K. Feldmann, E. Daltrozzo, and G. Scheibe, *Z. Naturforsch. B.* **22**, 722 (1967).

(5) relating the chemical shift parameter of the 6-proton, δ_H , and the charge density on the 6-carbon atom, ρ_c .²⁹ Q_H is a constant.

$$\delta_H = Q_H \rho_c \quad (5)$$

This was tested for the dihydrodiazepinium salts (**9a-e**). Q_H is approximately 36 ppm per electron and the correlation holds fairly well except for compound **9e**, which may be anomalous owing to crowding in the molecule caused by vicinal substitution.

C. ELECTROCHEMICAL CONSTANTS

Dihydrodiazepinium salts have been studied using single-sweep polarographic methods.³² Compounds **9a-d** all gave what are probably reversible, one-electron diffusion peaks with tetra-*n*-butylammonium perchlorate as supporting electrolyte. Compound **9e** was also studied by this method using tetra-*n*-butylammonium iodide as supporting electrolyte. In the latter case, although the peak may be reversible, the transition involves more than one electron.³²

The peak potential E_p is related to the half-wave potential which is in turn proportional to m_{m+1} for a reversible, diffusion-controlled wave of a given substance in a given solvent.³³ It was concluded *inter alia* that polarographic reduction of salts **9a-c** is different from that of salt **9d**.³² Because of the paucity of data the relation between E_p and m_{m+1} was not tested but a similar trend in E_p and m_{m+1} was observed for each of the three related compounds **9a-c**.³²

D. REACTIVITY TO ELECTROPHILIC ATTACK

Coulson free valences (F) (see Table III) calculated from the Hückel model indicate that, when there are phenyl groups substituted at positions 1 and 4 and methyl groups at positions 5 and 7, electrophilic substitution will take place at the ortho and para positions of the phenyl groups as well as at position 6 of the dihydrodiazepinium ring.³⁴ Similar results are suggested for 5,7-phenyl-disubstituted dihydrodiazepinium salts, with substitution occurring preferentially at position 6. Bromination and nitration of the 5,7-dimethyl-1,4-diphenyldihydrodiazepinium cation does indeed take place at the predicted sites. Bromination of 5,7-di-

³² A. Alexander, H. P. Cleghorn, and D. Lloyd, unpublished results.

³³ A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York, 1961.

³⁴ H. P. Cleghorn, unpublished results.

TABLE III

COULSON FREE VALENCES OF SOME DIHYDRODIAZEPINIUM PERCHLORATES

Compound	F_5	F_6	F_7	F_o^a	F_m^a	F_p^a
(9a)	0.339	0.404	0.339	—	—	—
(9b)	0.343 ^b	0.429	0.259 ^b	—	—	—
(9c)	0.225	0.454	0.225	0.451	0.394	0.422
(9e)	0.347	0.406	0.347	0.424	0.399	0.408

^a F_o , F_m , F_p refer, respectively, to *o*-, *m*-, and *p*-positions of phenyl ring.

^b F_5 and F_7 refer, respectively, to Me- and Ph-substituted positions.

phenyldihydrodiazepinium salts occurs solely at position 6 of the dihydrodiazepinium ring but nitration in nitric acid-sulfuric acid mixtures brings about substitution in the phenyl groups as well as in the dihydrodiazepinium ring, although with nitric acid alone the phenyl groups are not attacked.^{28,35} Coulson free valence indices do not explain the observed²⁷ electrophilic substitution at position 6 when positions 5 and 7 are unoccupied; in those cases (9f, 9g, 9h), and also for 9i, the calculations indicate $F_{5,7} > F_6$, thus predicting attack at position 5(7).

VI. Electrochemical Studies

The first reported electrochemical study on dihydrodiazepines was a potentiometric determination carried out on the 5,7-dimethyl derivative. A value of pK_a between 13 and 14 was obtained in this way.²¹ The technique has since been applied to 6-nitro-5,7-diphenyldihydrodiazepine, giving a pK_a of 6.7.³⁶ For other dihydrodiazepines with very high pK_a values, spectrophotometric methods have proved more convenient and often more accurate.²⁴

Polarographic reductions of dihydrodiazepinium salts have been carried out in *N,N*-dimethylformamide as solvent. Compounds 9a-d gave broad irreversible waves having half-wave potentials ($E_{1/2}$) approaching -2.0 V with respect to the mercury pool.³² Single-sweep polarographic studies in dimethylformamide using tetra-*n*-butylammonium perchlorate (TBAP) as supporting electrolyte gave reversible one-electron diffusion peaks for many of the salts, as shown in Table IV. In this table data are also recorded

³⁵ A. M. Gorrings, D. Lloyd, F. I. Wasson, D. R. Marshall, and P. A. Duffield, *J. Chem. Soc. C*, 1449 (1969).

³⁶ A. Alexander and H. P. Cleghorn, unpublished results.

from studies in which tetra-*n*-butylammonium iodide (TBAI) was used as supporting electrolyte, but the results appear to be less informative.³²

The results indicate that the introduction of electron-withdrawing groups lowers the numerical value of E_p . This also implies that the main interaction of phenyl groups at the 5(7)-positions is inductive, since conjugative interaction of such groups is of necessity electron-donating (see Lloyd *et al.*³⁷).

TABLE IV
POLAROGRAPHIC PEAK POTENTIALS (CATHODIC) FOR SOME
DIHYDRODIAZEPINIUM PERCHLORATES

Salt	R ⁴	R ⁵	R ⁶	R ⁷	R ¹	E_p^c (TBAI) (volts)	E_p^c (TBAP) (volts)
(9a)	H	Me	H	Me	H	No peaks	-1.57
(9b)	H	Me	H	Ph	H	No peaks	-1.28
(9c)	H	Ph	H	Ph	H	~-2.0	{ -1.12 -1.92
(9d)	Ph	H	H	H	Ph	No peaks	-0.84
(9e)	Ph	Me	H	Me	Ph	-0.54	
(9f)	H	Me	Br	Me	H	—	{ -1.00 -1.54
(9g) ^a	H	Me	Br	Me	Me	—	{ -0.95 -1.55
(9h)	H	Me	OMe	Ph	H	—	-1.24
(9i)	H	Me	H	Ph	Me	—	-1.29
(9j) ^a	H	Ph	Br	Ph	H	~-2.0	{ -0.85 -1.10 -1.93
(9k)	H	Ph	NO ₂	Ph	H	No peaks	{ -0.75 -1.08 -1.20
(9l)	H	Ph	NH ₂	Ph	H	{ -1.3 -2.0	{ -1.15 -2.0
(9m)	H	Ph	H	<i>p</i> -C ₆ H ₄ NH ₂	H	~-2.0	
(9n) ^b	Ph	H	NO ₂	H	Ph	-1.06	{ -0.58 -1.02 -2.0

^a Bromide salt.

^b Tetrafluoroborate salt.

^c E_p Cathodic potential at the maximum of the polarographic peak.

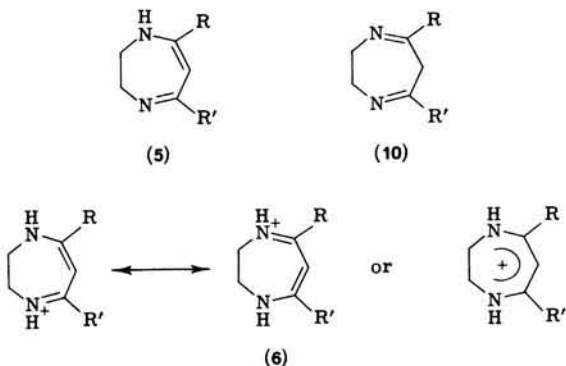
Polarographic reductions have also been carried out in aqueous ethanol over a pH range of 2-8.³⁸ It appears that the polarographic reduction of **9c** in acidic solution gives mainly ethylenediamine, benzylideneacetophenone, and benzylacetophenone. Reduction of **9d** gave dianilinoethane and the hexahydrodiazepine as the major identifiable products, although, under the conditions of the polarographic experiment, only a one-proton one-electron addition may occur in the initial step. Mechanistic schemes for these reductions have been suggested.³⁸

The 6-nitrodihydrodiazepinium perchlorate (**9n**) can also be reduced under these conditions. The main polarographic wave in this case arises from the reduction of the nitro group to a hydroxyamino group.³⁸

VII. Structure and Spectra

A. STRUCTURE

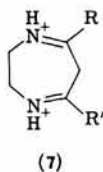
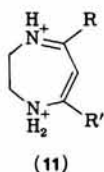
Dihydrodiazepine bases might have either the conjugated structure **5** or the nonconjugated structure **10**; all the spectroscopic evidence points to the former.^{8,12,18,20} Rapid tautomeric exchange of a hydrogen atom between the two nitrogen atoms takes place, however, since NMR spectra



in carbon tetrachloride, deuteriochloroform, or perdeuteriomethanol show that for symmetrically substituted dihydrodiazepines the 2 and 3 positions and also the 5 and 7 positions are, respectively, equivalent.^{20,30} The monocations must have the conjugated structure **6**; this was again confirmed by the NMR spectra.⁹ Protonation of the monocations might take

³⁸ H. P. Cleghorn, J. E. Gaskin, and D. Lloyd, *J. Chem. Soc. B*, 1615 (1971).

place at a nitrogen atom to give dications such as **11** or alternatively at the 6-position to give dications **7**. Spectroscopic evidence shows that the



latter is certainly the predominant species in solutions of dihydrodiazepines in strong acid,⁹ although hydrogen-deuterium exchange takes place in deuterio acids both at the nitrogen atoms and at the 6-position.^{8,18,20,25}

B. ELECTRONIC SPECTRA

The electronic spectra of dihydrodiazepinium salts are characterized by an intense absorption ($\epsilon = 15,000\text{--}25,000$) usually between 300 and 360 nm. The related bases absorb with somewhat reduced intensity at a slightly shorter wavelength. In the alkyl-substituted dications there is no appreciable absorption above 200 nm, but in the case of the 5,7-diphenyldihydrodiazepine there is a band at ~ 290 nm ($\epsilon = 23,500$); the changes are due to loss of the conjugated dihydrodiazepinium system when it is protonated to form a dication. This absorption in the dihydrodiazepinium monocations has been ascribed to a $\pi\text{--}\pi^*$ transition.^{29,30} It occurs at a similar wavelength and intensity to the $\pi\text{--}\pi^*$ transitions in open-chain *cis*-2-iminoenamines but not to those of pyrimidines, thus suggesting that there is no cyclic electronic interaction in the dihydrodiazepines.³⁰

Substituent groups have a generally regular effect on the position of the absorption maxima in dihydrodiazepinium cations. Thus methyl groups at the 1- and 4-, or 6-positions cause bathochromic shifts of +6 and +22 nm, respectively, whereas at the 5,7-positions they cause (hypsochromic) shifts of -4 nm.^{12,15} These effects are additive for multiply-substituted compounds and may be compared with similar shifts in azulenes, with methyl groups substituted at positions of high or low π -electron density causing, respectively, bathochromic or hypsochromic shifts. There are similar regular changes in the intensity of absorption, which is raised by methyl groups at the 1-, 4-, 5-, or 7-positions but lowered by a methyl group at the 6-position.¹²

Phenyl groups have a regular bathochromic effect, amounting to ~ 14 nm at the 5,7-positions and ~ 25 nm for each *N*-phenyl or 6-phenyl

group.^{14,16,31} These bathochromic effects are, however, diminished if there is a methyl group on a site next to the phenyl group, due to steric interference between the adjacent groups which forces the phenyl group far enough out of coplanarity with the dihydrodiazepinium ring to reduce electronic interaction between the rings.^{14,15}

Other substituent groups at the 6-position also make marked and fairly regular contributions to the UV spectra of dihydrodiazepinium salts. Halogen atoms, arylazo, alkoxy, and amino groups have marked bathochromic effects, lost in the case of amines when the amino group is protonated.^{16,26,28,35,39}

C. INFRARED SPECTRA

The infrared spectra of dihydrodiazepinium salts are complex but there are several characteristic bands.¹² In the 3000 cm^{-1} region ν_{NH} shows as a medium to strong band at $\sim 3500 \text{ cm}^{-1}$. Hydrogen atoms at the 5-, 6-, or 7-positions give rise to a weak $\nu_{\text{C-H}}$ band at 3050–3100 cm^{-1} ; alkyl $\nu_{\text{C-H}}$ bands at $\sim 2900 \text{ cm}^{-1}$ are also weak. When there are hydrogen atoms at positions 5 or 7 there is a fairly strong band at 1215–1255 cm^{-1} , which is absent if these positions carry substituents; they may be due to C—H deformations. All spectra of dihydrodiazepinium salts show three strong bands at 1610–1650 cm^{-1} , at 1510–1575 cm^{-1} and at 1305–1335 cm^{-1} , the first two apparently due to coupled multiple-bond stretching and the third to $\nu_{\text{C-N}}$.

The infrared spectra of dihydrodiazepine bases show bands at 3150–3190 cm^{-1} (NH), no normal C=N absorption, and a characteristic absorption between 1500 and 1600 cm^{-1} .

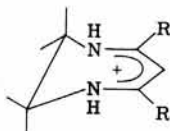
D. NUCLEAR MAGNETIC RESONANCE SPECTRA

The NMR spectra of dihydrodiazepines and their mono- and dications accord completely with the assigned structures.^{9,20,29,30,37,40} The most characteristic feature of the spectra of the dihydrodiazepinium salts is the markedly different positions at which protons at the 5- and 7-positions (τ 2.4–2.6 for *N*-unsubstituted compounds) and at the 6-position (τ 4.0–5.0) appear. This can be correlated with the large difference in nucleophilicity of these sites, as discussed later in this chapter (Section VIII). Signals due to groups at the 5-, 6-, or 7-positions all appear at higher field in the spectra of dihydrodiazepine bases than in the cations due to the loss of positive charge.

³⁹ C. Reichardt, *Ann. Chem.* **746**, 207 (1971).

⁴⁰ E. Daltrozzo and K. Feldmann, *Tetrahedron Lett.*, 4983 (1968).

A detailed study of the NMR spectra, in particular of coupling constants, has shown that the dihydrodiazepinium cations exist in half-chair conformations (12).³⁷ These half-chair conformations undergo rapid inversion at room temperature. Methylene groups at the 2- and 3-positions appear



(12)

as singlets at room temperature but as AA'BB' multiplets at lower temperatures. The coalescence temperatures, which occur at about -20° to -40° , appear to depend on the bulk of substituents in the methine portion of the ring, but electronic factors appear to have little effect.³⁷ This is thus a further example of the steric effects of substituents on the properties of this system. (Compare Sections IV and VII,B).

Signals due to 5(7)-phenyl groups, which in the absence of neighboring substituent groups give multiplet signals, appear instead as singlets if vicinal methyl groups are present.^{14,37} This may again be ascribed to crowding, which forces the phenyl groups out of the plane of the dihydrodiazepine ring in the latter cases.

¹³C NMR studies also emphasize the difference between the 6- and the 5,7-positions, the signals for 5,7-C appearing ~ 80 ppm. downfield from the 6-C signals.^{40a}

VIII. Electrophilic Substitution Reactions

A. GENERAL

Perhaps the most characteristic reaction of dihydrodiazepinium salts is their electrophilic substitution at position 6. Thus they are readily deuteriated,^{20,25,41,42} halogenated,^{9,15,26,35} and nitrated,^{28,43,44} and couple with diazonium salts.⁴⁵ Reaction occurs under conditions similar to those

^{40a} D. Lloyd, H. McNab, and D. R. Marshall, unpublished results.

⁴¹ R. P. Bell and D. R. Marshall, *J. Chem. Soc.*, 2195 (1964).

⁴² C. Barnett and J. Warkentin, *J. Chem. Soc. B*, 1572 (1968).

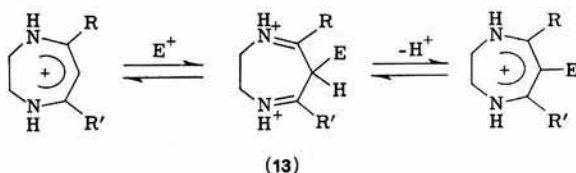
⁴³ A. M. Gorringer, D. Lloyd, D. R. Marshall, and L. A. Mulligan, *Chem. Ind. (London)*, 130 (1968).

⁴⁴ C. Barnett, *Chem. Commun.*, 637 (1967); *J. Chem. Soc. C*, 2436 (1967).

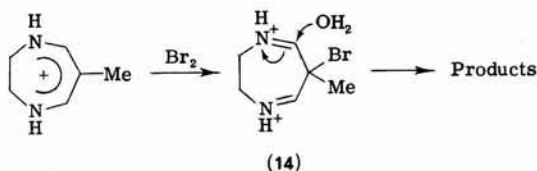
⁴⁵ E. M. Grant, D. Lloyd, and D. R. Marshall, *Chem. Commun.*, 1320 (1970).

used for benzene derivatives. Indeed the kinetics of the halogenation^{41,46} and nitration⁴⁶ reactions closely resemble those of benzenoid compounds, in the case of halogenation resembling those for activated benzene derivatives, such as phenols or amines. Kinetic studies indicate that the dihydrodiazepinium cation is indeed involved in these electrophilic substitutions, so that the nitration reaction represents a rare example of electrophilic attack by a cation on another cation.

The mechanism for these electrophilic substitution reactions involves formation of a dication intermediate **13** which, as in the case of benzenoid substitution reactions, loses a proton and reverts to the original stable system.



Similar stable intermediate dication structures cannot be drawn for electrophilic attack at the 5- and 7-positions. This is reflected in the enormous difference in reactivity toward electrophiles between the 6-position and the 5- and 7-positions.^{25,27} Kinetic studies of the bromination²⁷ and deuteration²⁵ of dihydrodiazepines and their salts indicate a ratio of reactivities of at least $1:10^9$, and probably greater. Indeed 6-methyldihydrodiazepinium salts undergo attack by bromine at the 6-position, despite the presence of the substituent group at that position, rather than at the 5(7)-position.²⁷ The resultant products are hydrolysis products since the dication intermediate (**14**) has no mesomeric stabilization and cannot gain such stabilization by loss of a proton, and, as a bisiminium salt, is readily hydrolyzed. Similarly, when 6-methyldihydrodiazepinium



salts are kept in deuteriotrifluoroacetic acid for up to 10 days no hydrogen-deuterium exchange can be detected at the 5- and 7-positions.²⁵

⁴⁶ D. Lloyd and D. R. Marshall, unpublished results; paper presented at Chemical Society Autumn Meeting, York, 1971.

Because of their "aromatic-like" reactivity the dihydrodiazepinium salts were described⁴ as "quasi-aromatic" compounds, a term which had previously been used to describe "nonaromatic" compounds which none the less showed "aromatic" chemical properties.⁴⁷ More recently it has been suggested^{5,6} that the tendency to undergo substitution rather than addition reactions might be termed "meneidic" or "regenerative" rather than "quasi-aromatic" owing to the confusion of the parent term "aromatic." Dihydrodiazepinium salts are thus examples of compounds having meneidic or regenerative character.

B. REACTION KINETICS

The similarity of behavior between the meneidic dihydrodiazepines and their salts and activated benzene derivatives, such as anilines and phenols, extends to reaction mechanisms, as indicated by kinetics. In aqueous solution bromination is a bimolecular reaction between dihydrodiazepinium cations and bromine molecules.^{27,41} The leaving bromide ion is still present in the transition state and, as in many (but not all) brominations of activated benzene derivatives, the rate-determining step is the initial attack which leads to formation of the intermediate σ -complex (**13**). Steric factors play a large part in the rates of bromination of dihydrodiazepinium salts in methanol, reaction being slower when large substituents are present at the adjacent 5- and 7-positions.^{47a} Substituents further removed from the site of bromination may also affect the rate.^{47a}

The initially produced 6-bromo derivative can be further brominated to give a 6,6-geminally dibrominated species.⁴¹ This reaction too begins by attack of bromine on the bromodihydrodiazepinium cation (though at a very much slower rate), but a reciprocal dependence of the rate upon the bromide ion concentration shows that the rate-determining step this time is not bromine attack, but decomposition of the intermediate. The reaction is accelerated by increase of pH, but the alternative explanation of a reaction involving bromination of bromodihydrodiazepine base is untenable. This effect of pH must arise from proton loss by the intermediate. The final products are those formed by hydrolysis of the unconjugated dibromo compound.

Iodination of dihydrodiazepines by iodine in buffered aqueous solution is particularly illuminating. Under most conditions the reaction rate is inversely proportional to the iodide concentration in a way which shows

⁴⁷ L. Mester, *J. Amer. Chem. Soc.* **77**, 4301 (1955).

^{47a} A. R. Butler, D. Lloyd, H. McNab, and D. R. Marshall, unpublished results; paper presented at Chemical Society Autumn Meeting, Norwich, 1973.

that the rate-determining step is removal of the leaving proton from the intermediate **13**. In agreement with this the reactions are subject to general base catalysis and show substantial kinetic deuterium isotope effects.⁴¹ By adjusting the base catalyst and iodide concentrations, however, it is possible to make competitive the rates of conversion of the intermediate to iodo product or the rates of reversion to the starting materials, and so to demonstrate that the mechanism is indeed a two-step mechanism.⁴⁸ In this the behavior is exactly like that of *p*-nitrophenol when it is iodinated.⁴⁹

Iodination too is accelerated by increase of pH.⁴⁸ There are two parallel reactions, one with a transition state of the composition of **13**, derived from dihydrodiazepinium cation, and a second related to the first by loss of a proton. As both reactions are generally base-catalyzed, this proton is an N—H proton. It is, however, impossible in principle to say whether the proton loss takes place before or after iodination, because the iodinations are slow enough for all steps prior to transition-state formation to be effectively in equilibrium with one another. This situation nevertheless allows us to treat the rate via the second reaction pathway as a rate of iodination of dihydrodiazepine base by iodine in a mechanism precisely

TABLE V

RELATIVE REACTIVITIES IN AQUEOUS HALOGENATION AT 25°C

Substrate	Iodination ($k_{\text{HPO}_4^{2-}}$)	Bromination (k_{Br_2})
Phenoxide anion	2.2×10^6 ^a	—
5,7-Dimethyldihydrodiazepine base	1.5×10^6	—
Aniline	3.0×10^2 ^b	$\sim 10^9$ ^c
5,7-Dimethyldihydrodiazepinium cation	2.0×10^{-2}	4.4×10^6
Phenol	—	1.8×10^5 ^d

^a Berliner.⁵⁰^b Berliner.⁵¹^c Bell and Ramsden.⁵²^d Bell and Rawlinson.⁵³

⁴⁸ D. Lloyd and D. R. Marshall, paper presented at Chemical Society Heterocyclic Group Meeting, London, January 1970.

⁴⁹ E. Grovenstein and N. S. Aprahamian, *J. Amer. Chem. Soc.* **84**, 212 (1962).

⁵⁰ E. Berliner, *J. Amer. Chem. Soc.* **73**, 4307 (1951).

⁵¹ E. Berliner, *J. Amer. Chem. Soc.* **72**, 4003 (1950).

⁵² Value for *N,N*-dimethylaniline: R. P. Bell and E. Ramsden, *J. Chem. Soc.*, 161 (1958).

⁵³ R. P. Bell and D. J. Rawlinson, *J. Chem. Soc.*, 63 (1961).

like that of dihydrodiazepinium cation iodination, and so to compare the reactivities of dihydrodiazepine base and dihydrodiazepinium cation.

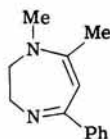
On this basis it is possible to compare directly the reactivities in aqueous bromination and iodination of dihydrodiazepine base and dihydrodiazepinium cation with those of para substitution in aniline, phenol, and phenoxide ion,⁴⁸ as shown in Table V.

The difference in reactivity between the dihydrodiazepine base and its cation is similar to that between phenoxide anion and phenol, and is associated with the change in charge type. Ease of σ -complex formation is not directly relevant.

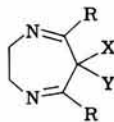
C. HALOGENATION AND PROTODEHALOGENATION

A wide variety of dihydrodiazepines and their monocations have been brominated by bromine in an organic solvent or by *N*-bromosuccinimide to give their 6-bromo derivatives.^{15,26,35} In most cases exclusively monobromination resulted, the exceptions being 1,4-diphenyldihydrodiazepinium salts which were also brominated in the phenyl rings. In contrast, 5-(7-)phenyl substituents are not brominated. The greater susceptibility to attack of phenyl groups at the 1- and 4-positions compared to phenyl groups at positions 5 or 7 is in accord with the low nucleophilicity of sites 5 and 7 compared to positions 1 and 4, and is clearly due to conjugation of the 1(4)-phenyl groups with the nitrogen atoms.

In one case bromination of a 5(7)-methyl group rather than substitution at the 6-position has been reported.³⁵ This occurred when 1,7-dimethyl-5-phenyldihydrodiazepine (**15**) was treated with bromine in methanol, and presumably results from the fact that, unlike *N*-unsubstituted dihydrodiazepines, this base has a fixed structure, incapable of tautomeric rearrangement, and that in this structure the 7-methyl group is activated by conjugation with the azomethine group.



(15)



(16)

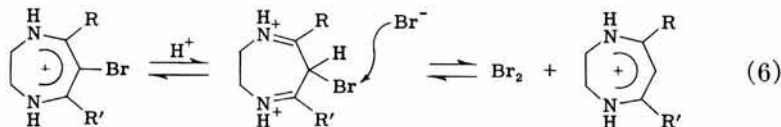
Dihydrodiazepinium salts can similarly be iodinated by the use of *N*-iodosuccinimide.³⁵ Alternatively, 6-iododihydrodiazepines are readily prepared by reaction of the corresponding 6-bromo compounds with sodium iodide in methanol.³⁵ (See also Section X.)

Chlorination is readily achieved by means of *N*-chlorosuccinimide

but aqueous work-up of a reaction between chlorine and 5,7-dimethyldihydrodiazepine gave only 3,3-dichloropentane-2,4-dione. It appears that chlorine readily dichlorinates the dihydrodiazepine to give a dichloro compound (**16**, R = Me, X = Y = Cl) which, having two azomethine groups but no stable delocalized electron system as in the parent compound, is very easily hydrolyzed.

Kinetic studies (see above) indicated that similar dibromination of dihydrodiazepines could take place in aqueous solution but the dibromo products were not isolated owing to their ready hydrolysis.⁴¹ The dibromo compound (**16**, R = Ph, X = Y = Br) and the bromochloro compound (**16**, R = Ph, X = Br, Y = Cl) were obtained³⁵ by bromination of the appropriate monohalodihydrodiazepines in dry benzene. These dihalo compounds were immediately debrominated to monohalodihydrodiazepines in dilute aqueous acid.

6-Bromodihydrodiazepinium halides, but not, for example, perchlorates or trifluoroacetates, are protodebrominated in strong acids.³⁵ Dilution with water of the solutions in strong acid causes reformation of the 6-bromo compounds but the debrominated products remain if the dilution is made with aqueous thiosulfate. These reactions are dependent on the equilibria of Eq. (6). In keeping with this mechanistic picture, 6-iododihydro-



diazepinium salts are dehalogenated more readily in acid than their bromo analogs,^{41, 54} whereas 6-chlorodihydrodiazepinium salts undergo dechlorination extremely slowly, if at all.⁵⁴

D. NITRATION

Dihydrodiazepinium salts are readily nitrated at the 6-position.^{28, 43, 44} Kinetic studies show that the dihydrodiazepinium monocation is indeed the substrate species involved in the reaction, the reagent being nitronium ion.⁴⁶

Nitric acid alone, or nitric acid-sulfuric acid mixtures are effective reagents for dihydrodiazepinium salts without phenyl substituents but nitric acid-sulfuric acid mixtures are unsuitable for phenyl-substituted compounds since under these conditions the phenyl as well as the di-

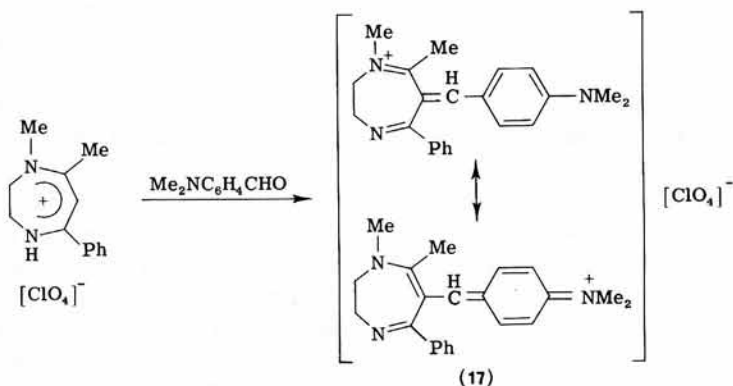
⁵⁴ E. M. Grant, D. Lloyd, and D. R. Marshall, unpublished results.

hydrodiazepinium rings are nitrated.²⁸ It has not been possible to isolate 6-nitrodihydrodiazepine bases owing to their ready hydrolysis.²⁸

E. REACTIONS WITH DIAZONIUM SALTS AND WITH *p*-DIMETHYLAMINO BENZALDEHYDE

Aryldiazonium salts react at once with dihydrodiazepinium salts and provide a further example of a reaction between two cations, but the coupling products are hydrolyzed very readily and the products isolated were α -arylazoderivatives of β -diketones.⁴⁵ 6-Arylazo-*N,N'*-disubstituted dihydrodiazepinium salts have, however, been obtained by condensation of mesoxaldialdehyde-2-phenylhydrazones with *N,N'*-disubstituted ethylenediamines.³⁹

A dihydrodiazepinium salt has also been coupled at its 6-position with *p*-dimethylaminobenzaldehyde to give the purple mesomeric product **17** which turns yellow in trifluoroacetic acid and is reprecipitated from such solutions by addition of methanol.



IX. Aminodihydrodiazepinium Salts

Nitro substituents in dihydrodiazepinium salts can be reduced by means of iron and acetic acid without reduction of the dihydrodiazepinium ring; for example, *p*-aminophenyl-substituted dihydrodiazepinium salts have been obtained in this way.²⁸ Although 6-nitro groups can also be reduced by metal and acid, it is not a satisfactory method for the preparation of 6-aminodihydrodiazepinium salts since the products apparently form complexes with the metal. 6-Amino derivatives are most conveniently prepared by catalytic reduction of the related nitro compound using either

cyclohexene and palladium-charcoal or hydrogen and palladium-charcoal.^{28,54,55}

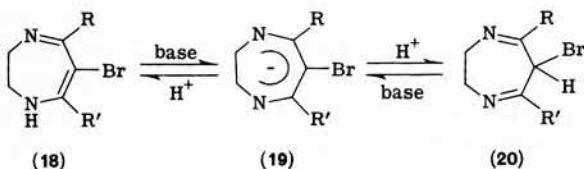
6-Aminodihydrodiazepinium salts are stable, but it has proved impossible to isolate the bases. The salts react readily with benzaldehydes to form stable anils which can be reduced to arylamino derivatives by sodium borohydride; this reagent also does not react with the dihydrodiazepine ring.^{28,55}

Reaction of 6-aminodihydrodiazepinium salts with sodium nitrite and acid produced stable solids with peaks in their IR spectra at 2200 cm^{-1} characteristic of aromatic and heteroaromatic diazonium salts.^{28,54,55} These diazonium salts could be converted into 6-chlorodihydrodiazepines.^{28,54,55} With alcohols or potassium iodide the diazonium group was replaced by a hydrogen atom; in the latter case it is likely that a 6-iodo compound was formed which was then protodeiodinated in the acid conditions.⁵⁴

X. Reactions of 6-Halodihydrodiazepines with Nucleophiles

As mentioned in Section VIII, 6-iododihydrodiazepines may be prepared by reaction of their 6-bromo analogs with sodium iodide in methanol.³⁵ Similarly, 6-bromodihydrodiazepines react readily with methoxide ions to give the corresponding 6-methoxy derivatives.^{26,35} Other 6-alkoxy-, 6-aryloxy-, and 6-aminodihydrodiazepines have been prepared by nucleophilic substitution.³⁵

This ready nucleophilic substitution is surprising, since in the normal tautomeric form **18** the 6-position should be deactivated towards nucleophilic attack; indeed, as discussed in Section VIII, this position is a site where electrophilic substitution takes place readily. It is possible that in the presence of base prototropic rearrangement via the dihydrodiazepenide anion **19** to the tautomer **20** takes place. Although the equilibrium concentration of **20** is likely to be very small it would be strongly electrophilic at the 6-position owing to the effects of the bromine atom and the two azomethine groups, and it could well be the reactive species in the nucleophilic substitution of the bromine atom. A tautomer of this structure

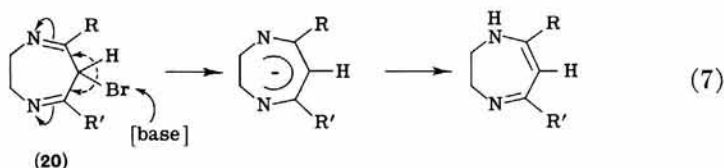


⁵⁵ A. M. Gorringe, D. Lloyd, and D. R. Marshall, *Chem. Ind. (London)*, 1160 (1968).

has never been observed in the case of dihydrodiazepines although it represents the normal structure of 2,3-benzo-1,4-diazepines.⁵⁶

In many cases reaction of 6-bromodihydrodiazepines with nucleophiles does not lead to the normal substitution products but instead the bromine atom is replaced by a hydrogen atom.³⁵ It has been shown³⁵ that debromination and nucleophilic substitution are competing reactions rather than that nucleophilic substitution precedes the introduction of the hydrogen atom. The dihydrodiazepines may themselves act as bases to bring about bromine-hydrogen exchange, for when some bromodihydrodiazepines were heated in an inert solvent, slow replacement of the bromine by hydrogen was observed.³⁵

Although the mechanism of this reaction is uncertain it seems likely that the bisazomethine tautomer **20** is again involved, nucleophilic attack on the bromine atom by base leading to an anion which, in turn, extracts a proton from the solvent or from another diazepine molecule [Eq. (7)].³⁵



The involvement of this tautomer is particularly suggested by the fact that under identical conditions *N*-methyldihydrodiazepines do not undergo this reaction.

The evidence available suggests that, in a general way, steric factors affect the course of the reaction. Increase in the size of substituents at positions 5 or 7 or in the size of the nucleophile appears to favor protodebromination over nucleophilic substitution. Furthermore it appears that 6-iododihydrodiazepines undergo protodeiodination rather than nucleophilic substitution irrespective of the size of the nucleophile or of 5(7)-substituents, whereas 6-chlorodihydrodiazepines are less susceptible to protodehalogenation.⁵⁴ Thus with thiourea 6-bromodihydrodiazepines undergo protodebromination, whereas 6-chlorodihydrodiazepines form 6-isothiuronium salts, in contrast to the normally more ready formation of isothiuronium salts from bromo compounds than from chloro compounds. It is not unreasonable that protodehalogenation should be favored for more bulky dihydrodiazepines or nucleophiles since this reaction has less steric demands than nucleophilic substitution. Similarly, both for

⁵⁶ I. L. Finar, *J. Chem. Soc.*, 4094 (1958); J. A. Barltrop, C. G. Richards, D. M. Russell, and G. Ryback, *ibid.*, 1132 (1959).

steric reasons and because of the relative ease of formation of halonium cations, protodehalogenation should be favored with respect to nucleophilic substitution in the order iodine > bromine > chlorine. The equilibrium between the conjugated form of the base (**18**) and the bis azomethine tautomer (**20**) may be somewhat more favorable to **20** if there are large 5(7)-substituents, since crowding between these substituents and the 6-substituent is thereby relieved.

ACKNOWLEDGMENT

We are grateful to Mr. H. McNab of the University of St. Andrews for reading the original draft of this chapter and offering constructive critical comments for its improvement.

1,5-Benzodiazepines

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AND

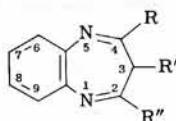
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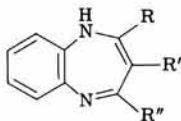
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I. Introduction

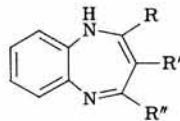
1,5-Benzodiazepines (1) are the 2,3-benzo-fused derivatives of the dihydrodiazepines of the previous Chapter. The reader should note that the numbering systems required (IUPAC; *Chemical Abstracts*) for the benzo series and the dihydro compounds proceed in opposite directions about the diazepine rings.



(1)



(2)



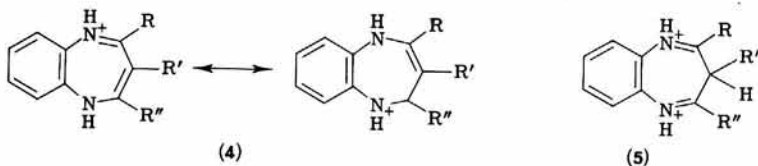
(3)

Therefore, positions 1,2,3,4, and 5 of the 1,5-benzodiazepines correspond to positions 1,7,6,5 and 4 respectively, in the monocyclic compounds.

This should be borne in mind when comparisons are made. Throughout this chapter the term "benzodiazepine" refers exclusively to the 1,5-diaza isomers.

Unlike the 2,3-dihydro-1,4-diazepines, benzodiazepines normally exist in the dianil form **1** rather than in the conjugated form **2**. In form **1** some extra stabilization is achieved by conjugation of the anil groups with the benzene ring. Cyclic conjugation as in form **2** may indeed destabilize the molecules since it involves either interaction of eight π -electrons around the seven-membered ring or, in form **3**, of 12 π -electrons around the periphery of the molecule; either of these formalizations are counter-Hückel systems.¹

Protonation of benzodiazepines leads to the formation, successively, of the monocations (**4**) and dications (**5**). The bases and dications are normally colorless or pale yellow, whereas the monocations are intensely



colored, frequently dark purple.

Benzodiazepines are less stable and more readily hydrolyzed than their dihydro counterparts discussed in the previous chapter.

II. Preparation of Benzodiazepines

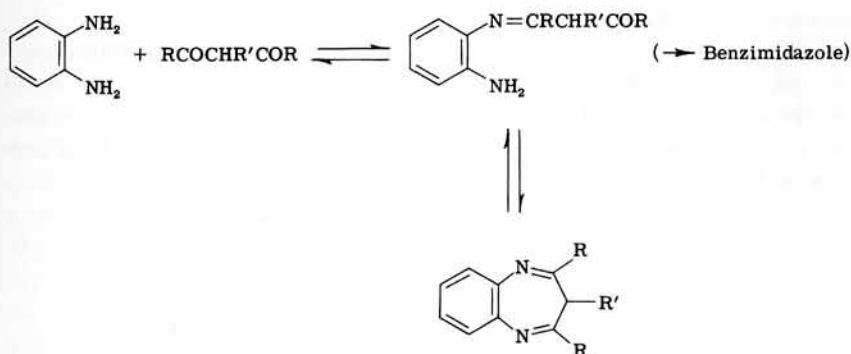
The first example of a benzodiazepine, the 2,4-dimethyl derivative (**1**, $R = R'' = \text{Me}$, $R' = \text{H}$) was prepared in 1907 by Thiele² by condensation of *o*-phenylenediamine with acetylacetone in ethanol-acetic acid. Addition of hydrochloric acid precipitated the purple hydrochloride.² The commonest method of preparation remains the reaction of *o*-phenylenediamine with β -dicarbonyl compounds.

Thus by reaction of *o*-phenylenediamine with the appropriate β -diketone

¹ D. Lloyd and D. R. Marshall, in "Aromaticity, Pseudo-aromaticity, Anti-aromaticity" (E. D. Bergmann and B. Pullman, eds.), p. 85. Israel Acad. Sci. Humanities, Jerusalem, 1971; *Angew. Chem.* **84**, 447 (1972); *Angew. Chem. Int. Ed. Engl.* **11**, 404 (1972).

² J. Thiele and G. Steimmig, *Ber.* **40**, 955 (1907).

the following benzodiazepines have been prepared: 2,4-dimethyl,²⁻⁷ 2,4-diphenyl,^{5,8,9} 2-methyl-4-phenyl,^{2,5} 2-methyl-4-anisyl (*m* and *p*),⁵ 2-methyl-4-(2'-selenienyl),¹⁰ 2,4-bis(bromomethyl),¹¹ 2-methyl-4-carboxy,¹² 2,3,4-trimethyl,^{7,13,14} 3-ethyl-2,4-dimethyl,¹⁴ and 3-(2'-benzimidazolyl)-2,4-dimethyl.¹⁵ As in the case of dihydrodiazepines, formation of 2(4)-aryl-substituted benzodiazepines is less simple than that of their alkyl analogs.⁵ The presence of a 3-substituent lowers the yield of benzodiazepine.⁷ It has been suggested⁷ that the formation of benzodiazepines involves the equilibria of Scheme 1.



Scheme 1

In the case, for example, of 2,3,4-trimethylbenzodiazepine, the equilibrium between the anil and benzodiazepine lies very much on the side of

³ B. Emmert and H. Gsottschneider, *Ber.* **66**, 1871 (1933).

⁴ G. Schwarzenbach and K. Lütz, *Helv. Chim. Acta* **23**, 1147 (1940).

⁵ J. A. Barltrop, C. G. Richards, D. M. Russell, and G. Ryback, *J. Chem. Soc.*, 1132 (1959).

⁶ S. Veibel and S. F. Hromadko, *Chem. Ber.* **93**, 2752 (1960).

⁷ J. O. Halford and R. M. Fitch, *J. Amer. Chem. Soc.* **85**, 3354 (1963).

⁸ I. L. Finar, *J. Chem. Soc.*, 4094 (1958).

⁹ S. Motoki, C. Urakawa, A. Kano, Y. Fushimi, T. Hirano, and K. Murata, *Bull. Chem. Soc. Jap.* **43**, 809 (1970).

¹⁰ Y. K. Yur'ev, N. N. Magdesieva, and V. V. Titov, *Zh. Org. Khim.* **1**, 163 (1965); *J. Org. Chem. USSR* **1**, 159 (1965).

¹¹ A. Becker, *Helv. Chim. Acta* **32**, 1584 (1949).

¹² J. Schmitt, *Ann. Chem.* **569**, 17 (1950).

¹³ S. B. Vaisman, *Tr. Inst. Khim. Khar'kov Gosudarst Univ.* **4**, 157 (1938); *Chem. Abstr.* **34**, 5847 (1940).

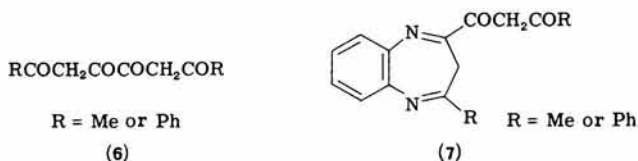
¹⁴ S. B. Vaisman, *Tr. Inst. Khim. Khar'kov Gosudarst Univ.* **5**, 57 (1940); *Khim. Referat. Zh.* **4**, 46 (1941); *Chem. Abstr.* **38**, 750 (1944).

¹⁵ T. N. Ghosh, *J. Ind. Chem. Soc.* **15**, 89 (1938).

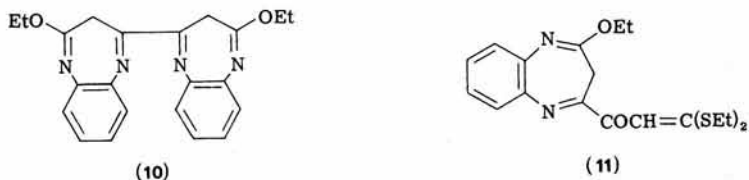
the anil because of steric hindrance due to the vicinal methyl groups in the benzodiazepine. Some benzimidazole is always formed as a by-product in the condensation reactions between *o*-phenylenediamine and β -diketones; if the ring-closure equilibrium does not favor cyclization to the seven-membered ring then competitive formation of benzimidazole becomes significant. No benzodiazepine has been obtained from *o*-phenylenediamine and 3,3-dimethylpentane-2,4-dione.^{7,13,14}

Mono-*N*-methyl-*o*-phenylenediamine reacts with acetylacetone to form the 1,2,4-trimethylbenzodiazepine but the yield is low; this has again been ascribed to destabilization of the ring-closed form due to steric interference between adjacent methyl groups.⁷

The reactions of several polyketones with *o*-phenylenediamine have been shown to provide benzodiazepines. Thus triacetyl methane gives 2,4-dimethylbenzodiazepine,⁵ while the tetraketones (6) gave the benzodiazepines (7) which did not react with a further equivalent of *o*-phenylenediamine to form bis benzodiazepines.⁸



The ketoketene acetals 8 and 9 react with *o*-phenylenediamine to give the benzodiazepines 10 and 11, respectively.¹⁶



2-Ethyl-3-methyl- and 2-*n*-butyl-3-*n*-propylbenzodiazepines have been prepared by condensation reactions involving β -ketoaldehydes and *o*-phenylenediamine,¹⁷ and a series of 2,3-cycloalkenobenzodiazepines was

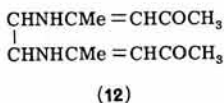
¹⁶ H. D. Stachel, *Chem. Ber.* **95**, 2172 (1962).

¹⁷ I. I. Lapkin and F. G. Saitkulova, *Zh. Org. Khim.* **6**, 450 (1970); *J. Org. Chem. USSR* **6**, 450 (1970).

obtained by reaction of *o*-phenylenediamine with 2-hydroxymethylene-cycloalkanones.¹⁸

A number of β -dialdehydes have been condensed with *o*-phenylenediamine to give 3-substituted benzodiazepines, for example, phenylmalondialdehyde,^{19,20} bromomalondialdehyde,²⁰ and nitromalondialdehyde.^{21,22} The parent unsubstituted 1,5-benzodiazepine has also been obtained in this way from a tetracetal of malondialdehyde.²³

These condensation reactions between *o*-phenylenediamine and β -dicarbonyl compounds are strongly pH-dependent. Thus in aqueous solution the maximum yield of benzodiazepine was obtained from acetylacetone in solutions buffered to pH $\sim 5^{24}$; the yield dropped to zero at pH greater than 8. In the reactions of aliphatic or alicyclic 1,2-diamines with β -diketones alternative products, e.g. **12**, are obtained in weakly alkaline solution. (See preceding chapter.) No such products have been isolated from the related condensation reactions involving aryl-*o*-diamines but an investigation²³ of the production of 2,4-dimethylbenzodiazepine from acetylacetone and *o*-phenylenediamine in buffered aqueous solutions showed that there was a minimum in the yield-pH curve at pH 6.0 and that the benzodiazepine was contaminated with another product which could not be obtained pure but whose IR spectrum was consistent with its being analogous to **12**.



Condensations between *o*-phenylenediamine and β -diketones also proceed in aprotic solvents. Thus alternative methods for the preparation of benzodiazepines have involved heating the hydrochloride of the diamine with a solution of the diketone in benzene,⁷ heating the amine and diketone in dry xylene containing toluene-*p*-sulfonic acid,⁵ and passing dry hydrogen chloride through an ethereal solution of the reactants.²³ In the latter method the benzodiazepinium dihydrochloride precipitates out and is converted into the monoacid salt by addition of water.

Substituted *o*-phenylenediamines have also been used for the prepara-

¹⁸ M. Weissenfels, W. Thust, and M. Mühlstädt, *J. Prakt. Chem.* **292**, 117 (1963).

¹⁹ H. Rupe and A. Huber, *Helv. Chim. Acta* **10**, 846 (1927).

²⁰ W. Ruske and E. Hüfner, *J. Prakt. Chem.* **18**, 156 (1962).

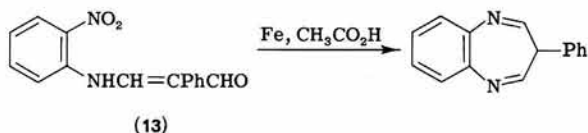
²¹ F. E. King and P. C. Spensley, *J. Chem. Soc.*, 2144 (1952).

²² W. H. Stafford, D. H. Reid, and P. Barker, *Chem. Ind. (London)*, 765 (1956).

²³ D. Lloyd, R. H. McDougall, and D. R. Marshall, *J. Chem. Soc.*, 3785 (1965).

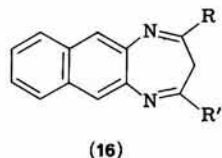
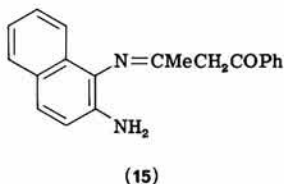
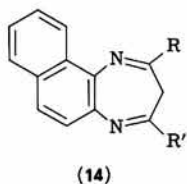
²⁴ C. A. C. Haley and P. Maitland, *J. Chem. Soc.*, 3155 (1951).

tion of benzodiazepines.^{23,25} Pure samples of substituted *o*-phenylenediamines, especially those having further electron-donating substituent groups present, are sometimes difficult to obtain. To overcome this problem, a modified procedure has been used²³ in which an *o*-nitro amine was reduced by means of hydrazine hydrate in the presence of Raney nickel;²⁶ immediately after decomposition of the excess of hydrazine hydrate the resultant solution of diamine was filtered directly into a solution of the diketone. The diamine was thus protected from oxidation throughout its preparation by the excess of hydrazine present. 6-Phenylbenzodiazepine was similarly prepared from the *o*-nitroamine (13) by its reduction with iron and acetic acid or tin and hydrochloric acid.¹⁹



Bisbenzodiazepines have been prepared by the condensation of the tetrahydrochlorides of 1,2,4,5-tetraminobenzene or 3,4,3',4'-tetraminobiphenyl with acetylacetone in the presence of base.²⁷

Naphthodiazepines have been obtained from diaminonaphthalenes. 1,2-Diaminonaphthalene condensed with acetylacetone,^{23,28} benzoylacetone²⁸ or dibenzoylmethane²⁸ in methanol-acetic acid, and addition of acid gave salts of the naphthodiazepines (14). In the case of benzoylacetone



a monoanil (15) could also be obtained if no acid were added.²⁸ This anil was rapidly hydrolyzed with concomitant formation of a 2-methylnaphthimidazole, but if treated with acid was converted into the naphthodiazepine (14, R = Me, R' = Ph).

2,3-Diaminonaphthalene also reacts with the appropriate diketones in alcohol-acetic acid followed by addition of mineral acid to give the naph-

²⁵ K. V. Levshina, T. A. Andrianova, and T. S. Safonova, *Zh. Org. Khim.* **5**, 175 (1969); *J. Org. Chem. USSR* **5**, 171 (1969).

²⁶ D. Balcom and A. Furst, *J. Amer. Chem. Soc.* **75**, 4334 (1953).

²⁷ R. L. Williams, J. Schuller, and D. Lloyd, *J. Heterocycl. Chem.* **5**, 147 (1968).

²⁸ W. Ried and W. Höhne, *Chem. Ber.* **87**, 1801 (1954).

thodiazepines (**16**, $R = R' = \text{Me}$; $R = \text{Me}$, $R' = \text{Ph}$; $R = R' = \text{Ph}$).^{23,29} If no acid is added, acetylacetone and benzoylacetone give anils corresponding to **15** but dibenzoylmethane does not condense at all.²⁹ It appears that in the absence of acid catalysis, aryl ketones are insufficiently reactive to condense with the diaminonaphthalenes.

2,3-Amino-1,4-naphthoquinone only gave monoanils with β -diketones, even in the presence of mineral acid.³⁰

An alternative approach to the synthesis of benzodiazepines involves the reaction of β -chlorovinyl carbonyl compounds with *o*-phenylenediamine. In the first example methyl β -chlorovinyl ketone was used to obtain 5-methylbenzodiazepinium chloride.³¹ An extensive investigation has been made of the use of β -chlorovinylaldehydes for the preparation of 2,3-substituted benzodiazepines.^{32,33} The preferred conditions for reaction were in alcoholic hydrogen chloride. By this means a variety of 2-aryl-, 2,3-cycloalkeno-, and 2,3-diarylbenzodiazepines was prepared. If no acid is present an uncyclized anil results, formed by condensation of one amino group with the aldehyde. Since the β -chlorovinylaldehydes are themselves readily obtained by reaction of α -methylene ketones with phosphoryl chloride and *N,N*-dimethylformamide or *N*-methylformanilide,³⁴ this provides an attractive route to 2,3-disubstituted benzodiazepines.

Benzodiazepines and naphthodiazepines (**16**) have also been prepared by addition and condensation of *o*-phenylenediamine, *N*-methyl- and *N*-phenyl-*o*-phenylenediamines, and 2,3-diaminonaphthalene with α -alkynyl ketones.^{34a}

Claims³⁵ that 2,3,4-triphenylbenzodiazepine is obtained by condensation of *o*-phenylenediamine with three equivalents of benzaldehyde were later³⁶ shown to be incorrect; the products were in fact benzimidazoles.

²⁹ W. Ried and E. Torinus, *Chem. Ber.* **92**, 2902 (1959).

³⁰ G. A. Efimova and L. S. Efros, *Zh. Org. Khim.* **3**, 162 (1967); *J. Org. Chem. USSR* **3**, 157 (1967).

³¹ W. Ruske and G. Grimm, *J. Prakt. Chem.* **18**, 163 (1962).

³² M. Weissenfels, *Z. Chem.* **4**, 458 (1964).

³³ M. Weissenfels, H. Schurig, and G. Hühsam, *Chem. Ber.* **100**, 584 (1967).

³⁴ Z. Arnold and J. Žemlička, *Próc. Chem. Soc.*, 227 (1958); *Coll. Czech. Chem. Commun.* **24**, 2385 (1959); Y. V. Quang, P. Cadot, and A. Willenart, *C. R. Acad. Sci.* **248**, 2356 (1959); W. Ziegenbein and W. Lang, *Chem. Ber.* **93**, 2743 (1960); **95**, 2321 (1962); K. Bodendorf and R. Mayer, *ibid.* **98**, 3554 (1965); J. M. F. Gagan, A. G. Lane, and D. Lloyd, *J. Chem. Soc. C*, 2484 (1970).

^{34a} W. Ried and E. König, *Ann. Chem.* **755**, 24 (1972).

³⁵ S. Weil and H. Marcinkowska, *Rocz. Chem.* **14**, 1312 (1934); *Chem. Abstr.* **29**, 6233 (1935); N. V. Subba Rao and C. V. Ratnam, *Current Sci. (India)* **24**, 299 (1955); *Chem. Abstr.* **50**, 12992 (1956).

³⁶ V. Veerangaiah, C. V. Ratnam, and N. V. Subba Rao, *Indian J. Chem.* **8**, 790 (1970).

In conclusion, it may be noted that attempts to obtain benzodiazepines by dehydrogenation either of 2,3-cyclohexano-2,3-dihydrodiazepines or of 2,3-benzotetrahydrodiazepines were unsuccessful.²³ Thus there is obviously no great energetic driving force toward the formation of benzodiazepines, which is in accord with their relatively low stability.

III. Spectra and Structure

All spectroscopic methods indicate that benzodiazepines exist in the dianil form **1** rather than in the isomeric conjugated forms **2** or **3**. However, it has been noted⁴ that when a solution of the purple 2,4-dimethylbenzodiazepinium hydrochloride was basified, a yellow solution resulted which, after a few seconds, turned colorless. This was attributed to initial formation of the conjugated base (**2**) which rapidly tautomerized to the normal dianil form.⁴

Thus the infrared spectra of a number of 2,4-dialkyl and 2,4-diarylbenzodiazepines show no peaks due to NH groups but do indicate the presence of a methylene group.^{5,8,20} This was confirmed by their NMR spectra,³⁷⁻³⁹ which also showed the presence of the 6-methylene group; this appears as a singlet at 37° at τ 7.30 in the case of the 2,4-dimethylcompound. In the monocation, however, a methylene signal is no longer evident but is replaced by a methine signal at $\tau \sim 2.5$, indicating that these cations have structure **4**^{39,40}; the spectrum also shows the symmetry of these salts as required by their mesomeric structure. Formation of the dication results in the reappearance of a methylene signal (τ 5.3 for the 2,4-dimethyl compound), showing that protonation of the monocation occurs at the 6-position rather than on nitrogen.³⁸ Both the 3-H and N-H undergo hydrogen-deuterium exchange in deuteriosulfuric acid.³⁸

Although the methylene signals of benzodiazepine bases appear as singlets at normal operating temperatures, at lower temperatures they give rise to double doublets.⁴¹ The results demonstrate that the benzodiazepine molecules take up boat conformations (**17**) which are, however, rapidly inverting at room temperature. For the compounds studied ΔG^\ddagger for inversion lay in the range 11–13 kcal mole.⁻¹ Phenyl groups at posi-

³⁷ J. A. Barltrop, C. G. Richards, and D. M. Russell, *J. Chem. Soc.*, 1423 (1959).

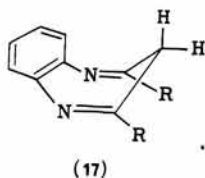
³⁸ H. A. Staab and F. Vögtle, *Chem. Ber.* **98**, 2701 (1965).

³⁹ W. J. Barry, I. L. Finar, and E. F. Mooney, *Spectrochim. Acta* **21**, 1095 (1965).

⁴⁰ W. Paterson and G. R. Proctor, *J. Chem. Soc.*, 485 (1965).

⁴¹ A. Mannschreck, G. Rissmann, F. Vögtle, and D. Wild, *Chem. Ber.* **100**, 335 (1967).

tions 2 and 4 cause an increase in ΔG^\ddagger compared with methyl groups; this



was ascribed to their having greater steric requirements in the transition state.⁴¹

Also in accord with their dianil structure, benzodiazepine bases have absorption bands in their electronic spectra at ~ 260 nm, similar to that of benzyldeneaniline.⁵ The intensities of these bands increase enormously in the monocations, which also show bands at ~ 500 nm which are responsible for the color of these salts.^{5,23,42} These long-wavelength bands disappear again in the dications which have maxima at ~ 260 nm, comparable to those in the bases.^{23,42} The long-wavelength absorption in the monocations is thus connected with the conjugated system present in this benzodiazepinium system. It is suggested that these long-wavelength absorptions are associated with $n-\pi^*$ transitions.⁴² This is supported by the fact that change from methanol to dimethyl sulfoxide as solvent causes a red shift in these maxima.⁴²

IV. Basicity

1,5-Benzodiazepines are very much weaker bases than 2,3-dihydrodiazepines. Furthermore the monocations require much less strong acid than do dihydrodiazepinium cations to convert them into the corresponding dications. The pK value for the base (1) to monocation (4) equilibria has been determined as 4.5 (2,4-dimethyl, potentiometric)^{4,43} and 5.76 (2,4-dimethyl, spectroscopic).⁴⁴ The presence of 2(4)-phenyl groups lowers the basicity still further.⁴⁴ The pK value for the monocation to dication equilibrium is ~ -1 . The benzodiazepinium cation is thus obviously a much less stabilized system than is the dihydrodiazepinium cation.⁴⁵ The low basicity of benzodiazepines is associated with this fact, with the interaction between the amine groups and the benzene ring, and also with the

⁴² H. P. Cleghorn, J. E. Gaskin, and D. Lloyd, *Rev. Latinoamer. Quim.* **2**, 103 (1971).

⁴³ G. Schwarzenbach and K. Lütz, *Helv. Chem. Acta* **23**, 1162 (1940).

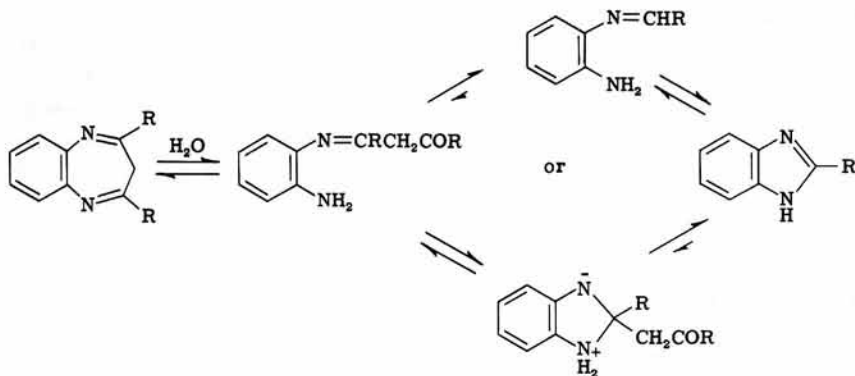
⁴⁴ S. Veibel and J. I. Nielsen, *Mat. Fys. Medd. Dan. Vid. Selsk.* **35**, No. 6 (1966).

⁴⁵ Cf. D. Lloyd and D. R. Marshall, *Chem. Ind. (London)*, 335 (1972).

necessity for tautomeric change of the base to the less favored conjugated form on cation formation. This last factor, of course, complicates the situation concerning the equilibrium $1 \rightleftharpoons 4$; this is really a combination of two equilibria $1 \rightleftharpoons 2 \rightleftharpoons 4$. A pK value of 9 has been assigned to the equilibrium $2 \rightleftharpoons 4$.⁴³

V. Stability and Hydrolysis

Benzodiazepines and benzodiazepinium salts undergo ring contraction to give benzimidazoles when heated in aqueous solution.^{2,5,18,23} This presumably proceeds via ring-opening of the seven-membered ring to form a monoanil, with subsequent hydrolysis and ring closure to form a five-membered ring (Scheme 2).

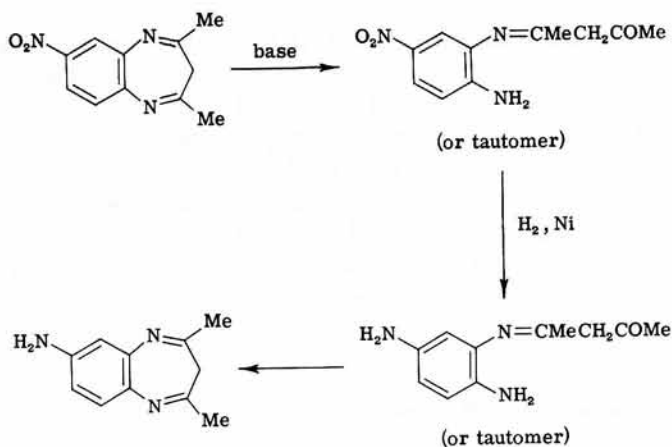


Scheme 2

The latter steps, essentially irreversible, control the overall reaction. Thus 2,4-dimethylbenzodiazepine gives acetone and 2-methylbenzimidazole,^{2,5,23} while 2-methyl-4-phenylbenzodiazepine gives a mixture of acetone, acetophenone, and 2-methyl- and 2-phenylbenzimidazoles.² The same ring contraction also ensues when aqueous solutions of benzodiazepines or their salts are kept at room temperature. It seems likely that with solutions of the salts, free base, present to some extent in equilibrium with the cation, may be the species involved in hydrolysis, since addition of traces of mineral acid greatly retards the rate of formation of benzimidazole.²³ Solutions in methanol are much more stable and solutions in methanol containing small amounts of mineral acid apparently keep indefinitely.²³

2,3-Disubstituted benzodiazepines appear to be more readily hydrolyzed than 2,4-disubstituted analogs.³³ Hydrolysis involves attack at the 2- or 4-position and is easier in the absence of a blocking substituent.

The concentration of ring-opened monoanil can only be small, and in the case of a number of benzodiazepines none could be detected spectroscopically.⁵ However the presence of electron-withdrawing substituents in the benzene ring assists nucleophilic attack at the 2(4)-position of the diazepine ring and in the case of 2,4-dimethyl-7-nitrobenzodiazepine the formation of the monoanil in methanolic alkali could readily be detected spectroscopically.^{23,25} Addition of acid led to instant reformation of the benzodiazepine.²³ Reduction of the anil with Raney nickel as catalyst led to the formation of 2,4-dimethyl-7-aminobenzodiazepine;²⁵ presumably the 4-nitro group is reduced to a 4-amino group which activates the 1-amino group to undergo ring closure with reformation of the diazepine ring (Scheme 3).



Scheme 3

Both naphtho[1,2]- and naphtho[2,3]diazepinium salts undergo similar ring contractions to form naphthimidazoles when heated in aqueous solutions.^{28,29}

Dry distillation of benzodiazepinium salts may also lead to formation of a ketone and a benzimidazolium salt.²³ A number of benzodiazepinium salts contain water of crystallization and this, or adsorbed water, must presumably participate in the reaction. It is possible that some of the quoted melting points of benzodiazepinium salts are in fact those of the benzimidazolium salts, interconversion having taken place at a lower temperature.

Further evidence for the presence of trace amounts of ring-opened benzodiazepine products in aqueous solution comes from the observations that such solutions give the reactions of the dicarbonyl compound and diamine from which the benzodiazepine is derived. Thus with phenylhydrazine, solutions of benzodiazepines form pyrazoles derived from the dicarbonyl fragment; for example, 2,4-dimethylbenzodiazepine gives rise to 3,5-dimethyl-1-phenylpyrazole.^{2,5,46} Similarly, diacetyl reacts with solutions of benzodiazepines to give quinoxalines derived from the diamine.^{5,46} The diazepine (7, R = Ph) gives 1,3,1',3'-tetraphenyl-5,5'-dipyrazolyl, but its methyl analog (7, R = Me) reacts only in the side chain to form a 2-methyl-4-pyrazolylbenzodiazepine.⁸

VI. Theoretical Studies

A Hückel model similar to that used for dihydrodiazepines has been applied to benzodiazepines.⁴² A correlation was obtained between the longest-wavelength transition and the lowest unoccupied Hückel molecular orbital parameter for benzo- and naphthodiazepines, which, it was suggested, indicated that these were $n-\pi^*$ transitions.

A correlation between the proton chemical shift parameter for the 3-proton of the diazepine ring and the charge density at the 3-carbon atom was also demonstrated.⁴² The results were quite distinct and separate from those obtained for dihydrodiazepines.

VII. Electrochemical Studies

Apart from a determination of the pK_a of the 2,4-dimethylbenzodiazepinium perchlorate⁴ (see Section IV) there have been no reliable electrochemical studies on 1,5-benzodiazepines, although the related series of 1,4-benzodiazepines has been studied extensively by electrochemical techniques.⁴⁷ Perhaps the main reason for the paucity of data on the presently reviewed compounds is their relative instability in aqueous solution which makes it difficult to determine whether observed values are due to the compound under examination or to decomposition products.

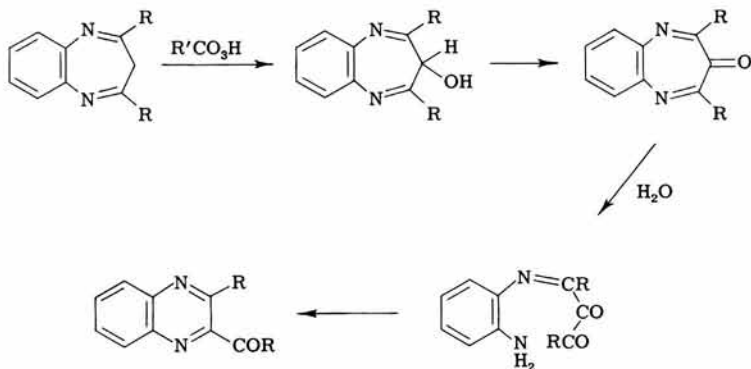
⁴⁶ J. A. Barltrop and C. G. Richards, *Chem. Ind. (London)*, 466 (1957).

⁴⁷ D. Halot, *Prod. Probl. Pharm.* **35**, 106 (1970).

VIII. Reduction and Oxidation

A benzodiazepine³⁷ and a naphtho[2,3]diazepine²⁹ have been reduced catalytically to tetrahydrodiazepines, but a naphtho[1,2]diazepine was reduced only very slowly over Raney nickel.²⁸ 2,4-Dimethyl-7-nitro-1,5-benzodiazepine was reduced catalytically with Raney nickel to give the corresponding aminobenzodiazepine without reduction of the diazepine ring.²⁵ 2,4-Dimethylbenzodiazepine was not reduced by lithium aluminum hydride.²³

2,4-Dimethylbenzodiazepine undergoes ring contraction to give 2-acetyl-3-methylquinoxaline on treatment with peracids,^{5,37,46} but 2,4-diphenylbenzodiazepine gives *o*-(benzoylamino)- α -hydroxyphenylacetanilide and not a quinoxaline.⁴⁸ It has been suggested that both oxidations initially involve attack at the 3-position to form a 3-hydroxy derivative.^{5,48} It is probable⁵ that this hydroxy compound is oxidized further to a 3-ketone, which then undergoes ring-opening followed by ring closure to give a quinoxaline, which may then suffer oxidative cleavage in the case of the diphenyl compound (Scheme 4).

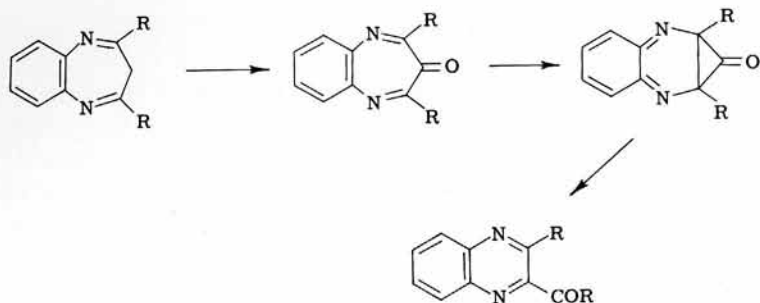


Scheme 4

Oxidation of solutions of benzodiazepines in benzene or acetic acid with a high-pressure mercury arc in oxygen also causes oxidative ring contraction to give quinoxalines.⁴⁹ Since hydrolytic cleavage is ruled out in this case a photolytic norcaradiene-type rearrangement of the intermediate ketone to a quinoxaline was suggested (Scheme 5).

⁴⁸ M. Matsumoto, A. Iio, and T. Yonezawa, *Bull. Chem. Soc. Jap.* **43**, 281 (1970).

⁴⁹ M. Matsumoto, Y. Matsumura, A. Iio, and T. Yonezawa, *Bull. Chem. Soc. Jap.* **43**, 1496 (1970).



Scheme 5

When a low-pressure mercury arc was used, 2,4-dimethylbenzodiazepine again gave a quinoxaline whereas 2,4-diphenylbenzodiazepine gave low yields of *o*-bis(benzoylamino)benzene and 2,4-diphenylbenzodiazepin-3-one.⁵⁰

Oxidation of 2,4-dimethylbenzodiazepine with ferric chloride led to the formation of 2,3-diaminophenazine.⁴⁶

IX. Substitution Reactions

2,4-Dimethylbenzodiazepine was mono-*N*-tosylated by means of toluene-*p*-sulfonyl chloride in pyridine.⁴⁰

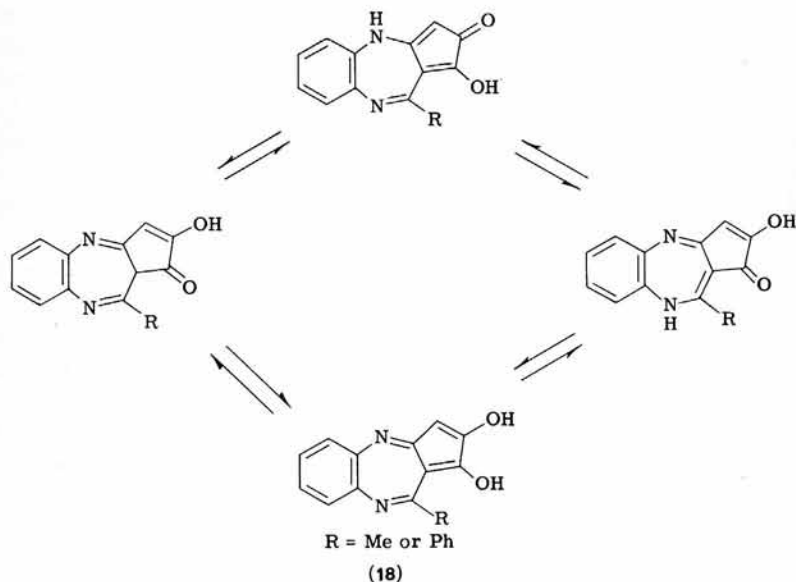
2,3-Dihydro-1,4-diazepinium salts readily undergo electrophilic substitution at the 6-position (see previous chapter) but attempts to nitrate 2,4-dimethylbenzodiazepinium salts, using either cupric nitrate or urea nitrate, produced only intractable tars, and bromination by means of bromine in acetic acid resulted in tetrabromination of the benzene ring only.²³ However, 2,4-diphenylbenzodiazepine coupled with *p*-nitrobenzenediazonium chloride to give a product which is probably the *p*-nitrophenylhydrazone of 2,4-diphenylbenzodiazepin-3-one. With sodium nitrite in acetic acid 2,4-dimethylbenzodiazepine gave a mixture of 2-methylbenzimidazole (formed by hydrolytic ring contraction), 2-acetyl-3-methylquinoxaline, presumably formed by nitrosation at the 3-position, followed by hydrolysis and rearrangement, and mono-*N*-nitrosated benzodiazepine.⁵

In basic conditions both the 3-methylene group and 2(4)-methyl groups should be susceptible to electrophilic attack owing to the adjacent imine groups. 2,4-Dimethylbenzodiazepine reacted with methyl iodide in liquid ammonia to give 2,3,4-trimethylbenzodiazepine.⁵

⁵⁰ T. Yonezawa, H. Matsumoto, and H. Kato, *Bull. Chem. Soc. Jap.* **41**, 2543 (1968).

With aryl aldehydes in the presence of base, 2,4-dimethylbenzodiazepine undergoes condensation at the methyl groups to give mono or bis benzylidene derivatives;^{5,44} 2,4-diphenylbenzodiazepine would not condense with benzaldehyde.⁹

2,4-Dimethyl- and 2-methyl-4-phenylbenzodiazepines reacted with oxalic ester at both the 3-position and 2-methyl group to give products



18.^{6,44,51} In the case of 2-methyl-4-phenyldiazepine, the 2-oxalyl derivative could also be obtained under different conditions.⁴⁴ Halogen atoms substituted on 2(4)-methyl groups readily undergo nucleophilic substitution; thus 2,4-bis(bromomethyl)benzodiazepine gives the 2,4-bis(iodomethyl) analog with sodium iodide in acetone.¹¹

X. 3-Oxo- and 3-Methylenebenzodiazepines

Derivatives of 3-oxo-benzodiazepines are of interest as hetero analogs of 4,5-benzotropone.

A 3-oxobenzodiazepine was not obtained until 1968, and then only in 1.4% yield, by oxidation of 2,4-diphenylbenzodiazepine by means of a

⁵¹ S. Veibel and J. I. Nielsen, *Chem. Ber.* **99**, 2709 (1966).

low-pressure mercury arc in an atmosphere of oxygen.⁵⁰ The infrared spectrum ($\nu_{C=O} = 1680\text{ cm}^{-1}$) does not suggest any marked dipolar character. This ketone is very unstable. In acid it readily loses carbon monoxide to form 2,3-diphenylquinoxaline.

Two alternative unsuccessful approaches to the preparation of 3-oxobenzodiazepines involved the 3-hydroxyimino- and 3-methylenebenzodiazepines.

3-Hydroxyimino-2,4-dimethylbenzodiazepine was prepared by condensation of *o*-phenylenediamine with 3-hydroxyiminopentane-2,4-dione in refluxing benzene.^{5,46} Attempts to hydrolyze the hydroxyimino group to a ketone group were unsuccessful. Mineral acids caused hydrolytic ring contraction to the oxime of 2-acetyl-3-methylquinoxaline, or under more vigorous conditions to 2-acetyl-3-methylquinoxaline itself.^{5,46} Acetic acid or oxalic acid produced 2-methylbenzimidazole,⁵ while alkali gave, among other products, *o*-phenylenediamine, its diacetyl derivative, 2-methylbenzimidazole, and 2-hydroxy-3-methylquinoxaline.^{5,46} When the hydroxyiminobenzodiazepine was heated with dilute acid and acetylacetone hydrolysis was followed by recombination of *o*-phenylenediamine with acetylacetone, the product being a 2,4-dimethylbenzodiazepinium salt.^{5,46} The hydroxyiminobenzodiazepine was also cleaved by hydroxylamine hydrochloride or hydrazine and its derivatives.⁵² Warm hydroxylamine hydrochloride gave the *anti*-oxime of 2-acetyl-3-methylquinoxaline but at room temperature gave the *cis*-oxime. Hydrazine cleaved the molecule to give *o*-phenylenediamine or, in the presence of acid, 2,3-diaminophenazine. A variety of acyl-, thioacyl-, and arylhydrazines gave some *o*-phenylenediamine and reasonable yields of the corresponding hydrazones of 2-acetyl-3-methylquinoxaline. It was suggested that reaction may proceed to some extent via partial hydrolysis of the benzodiazepine, but the nature of the by-products shows that some complete hydrolysis must also take place.⁵² A different reaction obtains when this diazepine is treated with either semicarbazide, thiosemicarbazide or *N*-methylthiosemicarbazide, the hydroxyimino group being replaced by the corresponding semicarbazone group.⁵³

2,4-Dimethyl-3-(diphenylmethylene)benzodiazepine was prepared by condensation of *o*-phenylenediamine with 3-(diphenylmethylene)pentane-2,4-dione in ethanol-acetic acid.⁹ 3-Methylenepentane-2,4-diones monosubstituted in the methylene group do not condense under these

⁵² C. N. O'Callaghan and D. Twomey, *J. Chem. Soc. C*, 600 (1969).

⁵³ V. C. Barry, M. L. Conalty, C. N. O'Callaghan, and D. Twomey, *Proc. Roy. Irish Acad., Sect. B* **65**, 309 (1967).

conditions.⁹ 3-Benzylidenepentane-2,4-dione on reaction with *o*-phenylenediamine in piperidine gave 2-phenylbenzimidazole together with some 2,4-dimethylbenzodiazepine, possibly formed by hydrolysis of initially formed 3-benzylidene-2,4-dimethylbenzodiazepine;⁵ in ethanol-acetic acid the sole product was 2-phenylbenzimidazole.⁵

1-, 2-, and 3-Benzazepines

S. KASPAREK

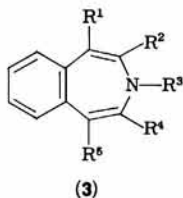
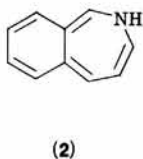
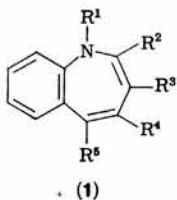
Research Division, Hoffmann-La Roche Inc., Nutley, New Jersey

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I. Introduction and Nomenclature

The fusion of a benzene ring at the *b*, *c*, and/or *d* edge of azepine gives rise to three isomeric benzazepines, i.e., **1** ($R^1-R^5 = H$), **2**, and **3** (R^1-

$R^5 = H$), respectively. Derivatives of these parent bases have been known since the early 1900s. The benzazepine skeleton has been found to be a component of natural products, e.g., *Amaryllidaceae* and *Papaveraceae* alkaloids. Derivatives of the benzazepines have been of interest to medicinal chemists for their wide range of biological activity.



A variety of names have been used in the literature to identify derivatives, especially perhydro derivatives, of **1** ($R^1-R^5 = H$), **2**, and **3** ($R^1-R^5 = H$): homotetrahydroquinoline, *asym*- and *sym*-homotetrahydroisoquinoline, homodihydrocarbostyryl, homodihydroisocarbostyryl, azabenzocycloheptene, benzohexamethyleneimine, and azabenzotropolone are examples of a few. *Chemical Abstracts* and "The Ring Index"¹ have designated **1** ($R^1-R^5 = H$), **2**, and **3** ($R^1-R^5 = H$) as 1*H*-1-, 2*H*-2-, and 3*H*-3-benzazepine, respectively, using the "indicated hydrogen" method to fix the position of the double bond in the heterocyclic ring of these compounds. These systematic names are now in common use. However, the trivial names can still be found even in the newest literature; entries of this kind are also found in the older indexes of *Chemical Abstracts*.

Although the chemistry of the benzazepines has received considerable attention over the past seven decades, only brief reviews have so far appeared; Moore and Mitchell² treated the chemistry of the benzazepines in the context of other seven-membered nitrogen heterocyclics and the synthesis of 3-benzazepines has been briefly reviewed by Gardent.³

It is the attempt of this review comprehensively to discuss the chemistry of the benzazepines; a short treatment of their biological activity has also been included.

It is hoped that all major papers which appeared up to June 1972 have been cited. Original papers have been examined; only those which are quoted with a reference to *Chemical Abstracts* have been used as digested by *Chemical Abstracts*.

¹ A. M. Patterson, "The Ring Index." Amer. Chem. Soc., Washington, D. C., 1960.

² J. A. Moore and E. Mitchell, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 9, Chapter 3. Wiley, New York, 1967.

³ J. Gardent, *Chim. Ther.* 1, 146 (1966).

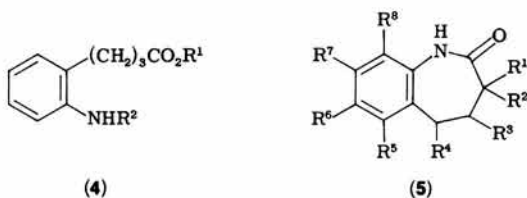
II. Methods of Synthesis

A. RING CLOSURE, C—N TYPE

Ring closure with the formation of a carbon–nitrogen bond, of the types A–E shown in Fig. 1, has been used to synthesize derivatives of 1-, 2-, and 3-benzazepines, with aminocarboxylic acids, amino halides, dihalides, dinitriles, dicarboxylic acids, and carboxylic acid diamides as starting materials. The yields were generally fair to good. In some cases preferential formation of a five- or six-membered ring was observed.

1. 1-Benzazepines

The first compound in the 1-benzazepine series was prepared by von Braun,⁴ who observed that 4-(2-aminophenyl)butyric acid (4, $R^1 = R^2 = H$), when freed from its salts, spontaneously cyclized to give 5 ($R^1-R^8 = H$) almost quantitatively. The spontaneity of this ring closure was later



questioned⁵ when it was claimed that only heating the acid above its

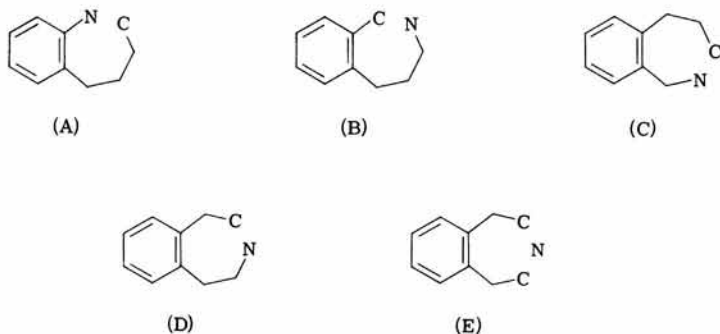
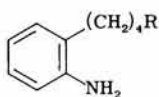


FIG. 1. Benzazepine formation by carbon–nitrogen ring closure.

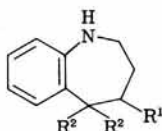
⁴ J. von Braun, *Chem. Ber.* **40**, 1834 (1907).

⁵ G. Schroeter, A. Gluschke, S. Goetzky, J. Huang, G. Irmisch, E. Laves, O. Schrader, and G. Stier, *Chem. Ber.* **63**, 1308 (1930).

melting point gave the lactam. It was not possible⁴ to cyclize the acylated acid **4** ($R^1 = H$; $R^2 = C(Ph)$). An attempt to convert the hydrochloride salt of **6** ($R = NH_2$) into **7** ($R^1 = R^2 = H$) by distillation failed. However, heating **6** ($R = Cl$) with alkali gave a good yield of **7** ($R^1 = R^2 = H$);



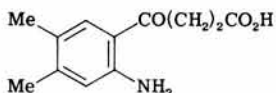
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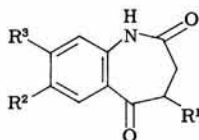
(7)

the latter could be also prepared directly from **5** ($R^1-R^8 = H$), without isolating the intermediates, by reducing the lactam with sodium in alcohol followed by treatment with excess of hydrochloric acid to give **6** ($R = Cl$) which was cyclized as mentioned above.⁶

The thermal cyclization of **8**, with or without solvent, afforded **9** ($R^1 = H$; $R^2 = R^3 = Me$). Recently, sodium hydride in dimethylformamide

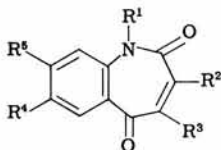


(8)

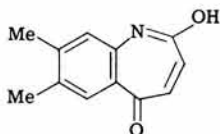


(9)

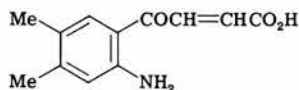
was used⁷ to cyclize less reactive derivatives of **8**. It was claimed that **10** ($R^1-R^3 = H$; $R^4 = R^5 = Me$) or its lactim (**11**) was obtained from **9** ($R^1 = H$; $R^2 = R^3 = Me$) by bromination followed by dehydrobromination; however, the structure proof of **10** ($R^1-R^3 = H$; $R^4 = R^5 = Me$) was in doubt.^{7a} A later attempt to prepare **10** ($R^1-R^3 = H$; $R^4 = R^5 = Me$) by the lactamization of **12** was not successful.⁸ The reductive cyclization



(10)



(11)



(12)

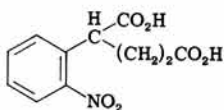
⁶ J. von Braun and B. Bartsch, *Chem. Ber.* **45**, 3376 (1912).

⁷ J. Witte and V. Boekelheide, *J. Org. Chem.* **37**, 2850 (1972).

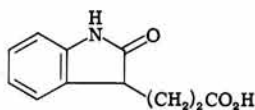
^{7a} A. H. Rees, *J. Chem. Soc.*, 3111 (1959).

⁸ A. H. Rees, *J. Chem. Soc.*, 3097 (1962).

of **13** with tin and hydrochloric acid⁹ gave the oxindole (**14**) instead of the lactam (**5**, $R^1-R^3 = H$; $R^4 = CO_2H$; $R^5-R^8 = H$). Carrying out the

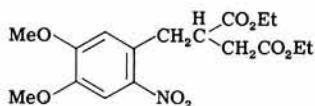


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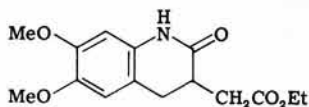


(14)

reductive cyclization of **15** over palladium on charcoal afforded¹⁰ the carbostyryl (**16**). When possible, a five- or six-membered ring is formed in preference to a seven-membered ring.^{9,10}



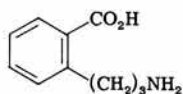
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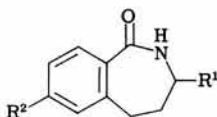
(16)

2. 2-Benzazepines

In contrast to the relatively mild reaction conditions required to form a lactam from **4** ($R^1 = R^2 = H$) it was necessary¹¹ to heat the acid **17** *in vacuo* at 190° to obtain **18** ($R^1 = R^2 = H$). The tetrahydrobenzazepine



(17)



(18)

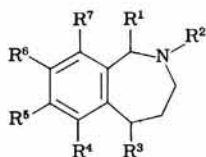
19 ($R^1-R^7 = H$) was prepared by treating **20** ($R^1 = Cl$, $R^2 = NH_2$, $R^3 = R^4 = H$) with excess aqueous sodium hydroxide.¹² Likewise, the phenolic benzazepine **19** ($R^1 = R^3 = R^6 = R^7 = H$; $R^2 = Me$; $R^4 = OH$; $R^5 = OMe$) was obtained in high yield when **20** ($R^1 = OH$; $R^2 = NHMe$; $R^3 = OCH_2Ph$; $R^4 = OMe$), prepared from 2-allylisovanilin, was treated

⁹ H. A. Lloyd and E. C. Horning, *J. Amer. Chem. Soc.* **76**, 3651 (1954).

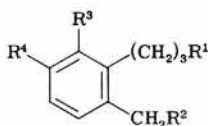
¹⁰ G. N. Walker, *J. Amer. Chem. Soc.* **78**, 3698 (1956).

¹¹ J. von Braun and H. Reich, *Ann. Chem.* **445**, 225 (1925).

¹² J. von Braun and F. Zobel, *Chem. Ber.* **56**, 690 (1923).

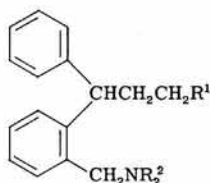


(19)



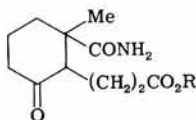
(20)

with thionyl chloride, then with sodium hydroxide, followed by debenzyla-
tion.¹³ In an alternative manner, **20** ($R^1 = R^2 = \text{Br}$; $R^3 = R^4 = \text{H}$)
reacted exothermically with dimethylamine in benzene to give the
methobromide of **19** ($R^1 = \text{H}$; $R^2 = \text{Me}$; $R^3\text{--}R^7 = \text{H}$).¹⁴ Using various
primary and secondary amines, a number of *N*-substituted 2-benzazepines
were thus obtained, the dihalides **20** ($R^1, R^2 = \text{Cl, Br}$; $R^3 = R^4 = \text{H}$)
being prepared from 1,3,4,5-tetrahydro-2-benzoxepin.^{15–17} The ring
closure of the diphenylmethanes **21** ($R^1 = \text{OEt, NMe}_2, \text{OH}$; $R^2 = \text{Me, CH}_2\text{Ph}$)
with hydrogen bromide, hydrogen chloride, or thionyl chloride

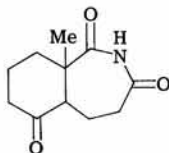


(21)

to give the appropriate quaternary salts of **19** ($R^1 = \text{H}$; $R^2 = \text{Me, CH}_2\text{Ph}$;
 $R^3\text{--}R^7 = \text{H}$) is the subject of two patents.¹⁸ The sublimation *in vacuo* of
the amide **22** ($R = \text{H, Me}$) afforded **23**.¹⁹



(22)



(23)

¹³ F. Caesar and A. Mondon, *Chem. Ber.* **101**, 990 (1968).

¹⁴ J. von Braun and W. Kaiser, *Chem. Ber.* **58**, 2162 (1925).

¹⁵ A. Rieche and H. Gross, *Chem. Ber.* **95**, 91 (1962).

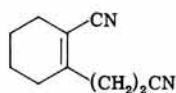
¹⁶ A. Rieche and E. Hoeft, *J. Prakt. Chem.* **17**, 293 (1962).

¹⁷ B. Belleau, *J. Med. Pharm. Chem.* **1**, 343 (1959).

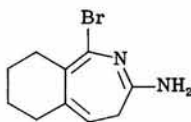
¹⁸ U. S. Patent 3,242,164; *Chem. Abstr.* **64**, 19576g (1966); U. S. Patent 3,225,031;
64, 9696g (1966).

¹⁹ H. H. Inhoffen and E. Prinz, *Chem. Ber.* **87**, 684 (1954).

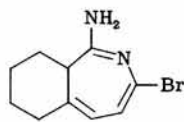
A previously described new synthetic method for the formation of the 3-benzazepine system^{20,21} was used to prepare 2-benzazepines.²² The dinitrile **24** gave with gaseous hydrogen bromide at 0° a fair yield of the 2-benzazepine **25**; this structure was assigned by NMR in preference to



(24)

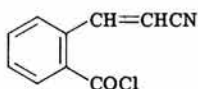


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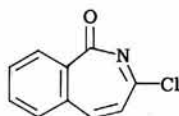


(26)

26. It is suggested that the carbon of the nitrile group at the unsaturated carbon in **24** is destined to bear the bromine atom while the nitrogen atom of the nitrile group at the saturated carbon becomes the amino group in the reaction product.^{22,23} An analogous intramolecular electrophilic attack at nitrogen is the basis of the ring closure of **27**, using hydrogen chloride as the catalyst,²⁴ to give **28**, and of a recently reported new

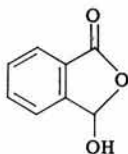


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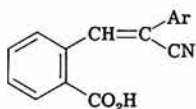


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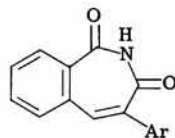
synthetic method for 2-benzazepin-1-ones. Phthalaldehydic acid (**29**) condenses with arylacetonitriles to give **30**, which is cyclized with poly-



(29)



(30)



(31)

phosphoric acid at 100° to **31**. Alternatively, **30** can be hydrogenated

²⁰ F. Johnson and W. A. Nasutavicus, *J. Heterocycl. Chem.* **2**, 26 (1965); U. S. Patent 3,205,222; *Chem. Abstr.* **63**, 13226 (1965); U. S. Patent 3,321,466; *Chem. Abstr.* **68**, 21857 (1968).

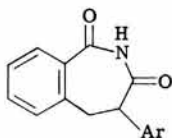
²¹ J. Gardent, *C. R. Acad. Sci.* **259**, 4724 (1964).

²² W. A. Nasutavicus and F. Johnson, *J. Org. Chem.* **32**, 2367 (1967).

²³ F. Johnson and R. Madronero, *Advan. Heterocycl. Chem.* **6**, 95 (1966).

²⁴ G. Simchen, *Angew. Chem. Int. Ed. Engl.*, 464 (1968).

and then cyclized to give **32**. The reaction presumably proceeds via the formation of an acylium ion from the benzoic acid moiety in **30**, which attacks the nitrogen of the nitrile group in molecules so constituted as

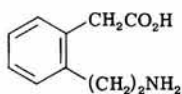


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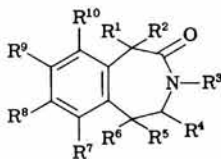
not to present any opportunity for forming five- or six-membered rings under acidic conditions.²⁵

3. 3-Benzazepines

Vigorous conditions were needed to achieve ring closure of **33** into **34** (R^1 – R^{10} = H). A comparison of the reactivity of aminocarboxylic acids,

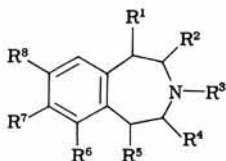


(33)



(34)

the three acids **4** (R^1 = R^2 = H), **17**, and **33** being among them, to give lactams led to the conclusion that the ease of lactam formation was dependent on the positions of the carboxyl and amino group. When these groups are attached to the benzene ring, cyclization takes place readily, while their reactivity decreases with increasing distance from the benzene nucleus.¹¹ The reduction of **34** (R^1 – R^{10} = H) with sodium in ethanol afforded **35** (R^1 – R^8 = H).²⁶

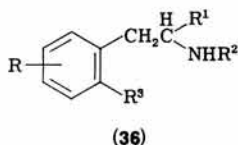


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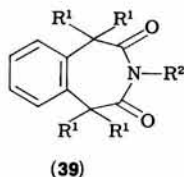
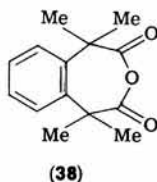
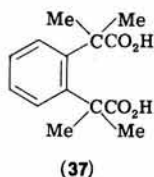
²⁵ G. N. Walker and D. Alkalay, *J. Org. Chem.* **36**, 461 (1971).

²⁶ J. von Braun and H. Reich, *Chem. Ber.* **58**, 2765 (1925).

The lactamization of aminocarboxylic acids is the last step in the recent synthesis of aromatic-substituted 3-benzazepines.²⁷ The appropriate phenethylamines (**36**, $R^1 = H, Me$; $R^2 = Ac$, $R^3 = H$) were converted by



standard methods into **36** ($R^1 = H, Me$; $R^2 = CH_2Ph$; $R^3 = CH_2CO_2H$), which was cyclized by refluxing in a high-boiling solvent with water removal to give very good yields of **34** ($R^1 = R^2 = R^5 = R^6 = H$; $R^3 = CH_2Ph$; $R^4 = H, Me$; $R^7, R^8, R^9, R^{10} = H, OMe, O-CH_2-O$). Thermal cyclization of aminocarboxylic acids is also employed in a synthesis of 3-benzazepines by an isoquinoline ring enlargement²⁸⁻³⁰ (see Section II,E). The dicarboxylic acid **37** or its anhydride **38** was heated with concentrated ammonia or *N,N*-dimethylethylenediamine to give



the imide **39** ($R^1 = Me$; $R^2 = H, CH_2CH_2NMe_2$).³¹

The reaction of **40** ($R = CH_2Br$) with primary aliphatic amines afforded the appropriate *N*-substituted 3-benzazepine.³² It has been reported¹² that **35** ($R^1-R^8 = H$) could not be prepared by eliminating ammonia from **40** ($R = CH_2NH_2$) and that the reduction of **40** ($R = CN$) with sodium in alcohol gave **41** and **40** ($R = CH_2NH_2$), respectively.³³ However, when the reduction of **40** ($R = CN$) was carried out over Raney nickel

²⁷ B. Pecherer, R. C. Sunbury, and A. Brossi, *J. Heterocycl. Chem.* **9**, 609 (1972).

²⁸ J. Chazerain, Thèse de l'Université de Paris (Pharmacie), 1962; *Ann. Chim. (Paris)* [13] **8**, 255 (1963).

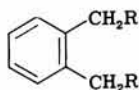
²⁹ M. Hamon, *C. R. Acad. Sci.* **255**, 1519 (1962); *Ann. Chim. (Paris)* [13] **10**, 213 (1965).

³⁰ G. Mahuzier and M. Hamon, *Bull. Soc. Chim. Fr.*, 687 (1969).

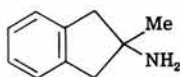
³¹ Ger. Offen. 1,921,861; *Chem. Abstr.* **72**, 31646 (1970).

³² French Patent 1,473,840; *Chem. Abstr.* **68**, 78160 (1968).

³³ J. von Braun, O. Kruber, and E. Danzinger, *Chem. Ber.* **49**, 2642 (1916).

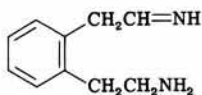


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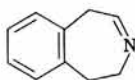


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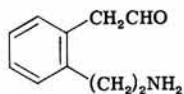
in alcohol saturated with ammonia, **35** ($R^1-R^8 = H$) was obtained in 83% yield.³⁴ Depending on reaction conditions **40** ($R = CH_2NH_2$) was also formed,³⁵ however, no **41** was isolated, contrary to the results using sodium in alcohol.³³⁻³⁶ It is suggested³⁴ that the hydrogenation proceeds via **42**, **43** or **42**, **44**, **43** \rightarrow **35** ($R^1-R^8 = H$). The hydrogenation can also be carried



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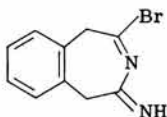


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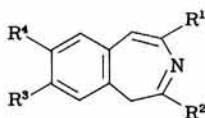


(44)

out over rhodium on alumina.³⁷ The ring closure of **40** ($R = CN$) was also achieved by inducing an intramolecular electrophilic attack of one nitrile group at the other. The treatment of the dinitrile with hydrogen bromide in acetic acid gives **45**, which, upon treatment with sodium bicarbonate, shifts the carbon-nitrogen double bond to give **46** ($R^1 = Br$;



(45)



(46)

$R^2 = NH_2$; $R^3 = R^4 = H$). The hydrolysis of the latter affords **39** ($R^1 = R^2 = H$). Hydrogen iodide can also be used for the reaction; however, hydrogen chloride is ineffective.^{20-22,38} The diamide (**47**) was pyrolytically cyclized at 295° into **39** ($R^1 = R^2 = H$) in good yield but in a high-boiling solvent only a poor yield was obtained.³⁹

³⁴ P. Rüggli, B. B. Bussemaker, W. Mueller, and A. Staub, *Helv. Chim. Acta* **18**, 1388 (1935).

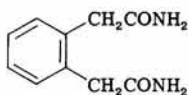
³⁵ P. Rüggli and A. Staub, *Helv. Chim. Acta* **20**, 925 (1937).

³⁶ J. H. Wood, M. A. Perry, and C. C. Tung, *J. Amer. Chem. Soc.* **73**, 4689 (1951).

³⁷ Swiss Patent 498,123; *Chem. Abstr.* **74**, 125489 (1971).

³⁸ J. H. Osborn, *Diss. Abstr.* **19**, 2475 (1959).

³⁹ J. O. Halford and B. Weissmann, *J. Org. Chem.* **17**, 1646 (1952).



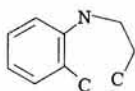
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B. RING CLOSURE, C—C TYPE

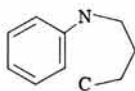
The formation of a carbon-carbon bond to construct the seven-membered ring of the benzazepines has been achieved by ring closures of the types F-L (Fig. 2). The Friedel-Crafts reaction (limited in the 1-benzazepine series), Dieckmann, acyloin, and aldol condensations, Bischler-Napieralski, Vilsmeier, and Pictet-Spengler-type reactions, and phenolic oxidative coupling have been used in the synthesis of the isomeric benzazepines.

1. 1-Benzazepines

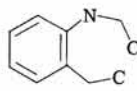
The Friedel-Crafts intramolecular acylation, so often used in the formation of six-membered heterocyclics, proved to be of less value in the synthesis of 1-benzazepines. Thus, when **48** ($n = 3$; $R^1 = \text{Ts}$; $R^2 = \text{OH}$, $R^3-R^5 = \text{H}$) was heated with polyphosphoric acid (PPA) the pyrrolidone **49** ($R^1-R^3 = \text{H}$) was the cyclized product. Similarly, the acid chloride



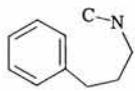
(F)



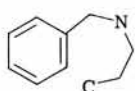
(G)



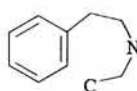
(H)



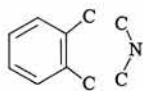
(I)



(J)

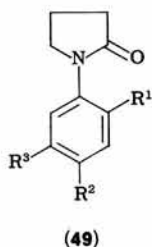
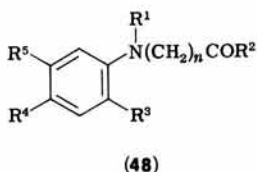


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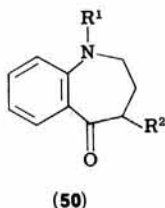


(L)

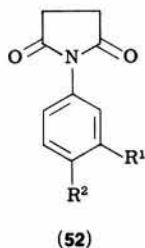
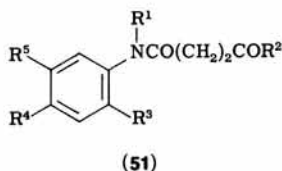
FIG. 2. Benzazepine formation by carbon-carbon ring closure.



48 ($n = 3$; $R^1 = \text{Ts}$; $R^2 = \text{Cl}$; $R^3\text{--}R^5 = \text{H}$) with aluminum chloride gave **49** ($R^1\text{--}R^3 = \text{H}$), in addition to *p*-tolyl phenyl sulfone, instead of the expected **50** ($R^1 = \text{Ts}$, $R^2 = \text{H}$).^{40, 41a, 42} Even the activation of the aromatic



ring in **48** ($n = 3$; $R^1 = \text{Ts}$; $R^2 = \text{OH}$, Cl ; $R^3 = \text{H}$; $R^4 = R^5 = \text{OMe}$) did not result in attack at the unsaturated carbon; instead ring closure at nitrogen took place with simultaneous migration of the tosyl group to give the sulfone **49** ($R^1 = \text{Ts}$; $R^2 = R^3 = \text{OMe}$).^{41a, 42} Similarly, **51** ($R^1 = R^3 = \text{H}$; R^4 , $R^5 = \text{H}$, Me ; $R^2 = \text{OH}$) gave the imide **52** ($R^1 = R^2 = \text{H}$) when treated with aluminum chloride or boron trifluoride



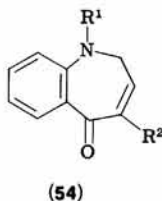
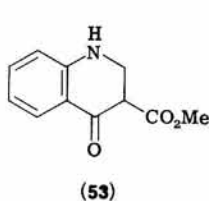
⁴⁰ B. D. Astill and V. Boekelheide, *J. Amer. Chem. Soc.* **77**, 4079 (1955).

⁴¹ (a) G. R. Proctor and R. H. Thomson, *J. Chem. Soc.*, 2302 (1957); (b) *ibid.* 2312 (1957); (c) W. H. Bell, E. D. Hannah, and G. R. Proctor, *ibid.*, 4926 (1964); (d) I. McCall, G. R. Proctor, and L. Purdie, *J. Chem. Soc. C*, 1126 (1970); (e) G. R. Proctor, W. I. Ross, and A. Tapia, *J. Chem. Soc., Perkin Trans. I*, 1803 (1972).

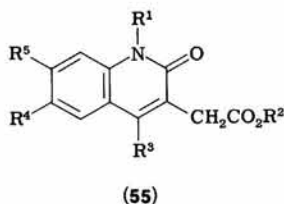
⁴² J. T. Braunscholtz and F. G. Mann, *J. Chem. Soc.*, 4174 (1957).

etherate.^{7a} Only very recently it has been shown by Proctor *et al.* that the use of phosphoryl chloride brings about the ring closure of **48** ($n = 3$, $R^1 = \text{Me}$, $R^2 = \text{OH}$, $R^3\text{--}R^5 = \text{H}$) to give a low yield of 5-chloro-1-methyl-2,3-dihydro-1*H*-1-benzazepine, which can be hydrolyzed to give the corresponding 1-benzazepin-5-one.^{41e}

The Dieckmann condensation proceeded satisfactorily with **48** ($n = 3$; $R^1 = \text{Me}$, Ac , Ts ; $R^2 = \text{OMe}$; $R^3 = \text{CO}_2\text{Et}$; $R^4 = R^5 = \text{H}$), using potassium *t*-butoxide in toluene,^{40,41b,43a} sodium in xylene,^{43b} or sodium hydride in dimethylformamide or toluene,^{41d,41e} to give **50** ($R^1 = \text{Me}$, Ac , Ts ; $R^2 = \text{H}$) in good yields, while the use of sodium or sodium hydride in benzene sharply decreased the yields.^{43b} On the other hand, attempted acyloin condensation ($\text{Na}/\text{C}_6\text{H}_6$) of **48** ($n = 2$; $R^1 = R^4 = R^5 = \text{H}$; $R^2 = \text{OMe}$; $R^3 = \text{CO}_2\text{Me}$) afforded^{41b} only the quinolone **53**. A reexamination^{41c} of the reaction showed that the condensation was sensitive to the purity of the solvent; using purified liquid ammonia it was possible, albeit in a low yield, to obtain **50** ($R^1 = \text{H}$; $R^2 = \text{OH}$) in addition to **53** and the keto ether **54** ($R^1 = \text{H}$; $R^2 = \text{OEt}$). Cooke and Haynes⁴⁴ claimed



that it was possible to cyclize **51** ($R^1 = R^4 = \text{H}$; $R^2 = \text{OMe}$; $R^3 = \text{CO}_2\text{Me}$; $R^5 = \text{H}$, OMe) into **9** ($R^1 = \text{CO}_2\text{Me}$; $R^2 = \text{H}$; $R^3 = \text{H}$, OMe) with finely divided sodium in toluene; however, the quinolone **55** ($R^1 = R^4 = \text{H}$; $R^2 = \text{Me}$; $R^3 = \text{OH}$; $R^5 = \text{H}$, OMe) was the major product formed.

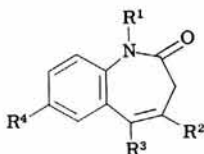


Recently, it has been shown that **51** ($R^1 = \text{Me}$, Et ; $R^2 = \text{OMe}$; $R^3 =$

⁴³ (a) J. T. Braunholtz and F. G. Mann, *Chem. Ind. (London)*, 266 (1957); (b) *J. Chem. Soc.*, 3377 (1958).

⁴⁴ R. G. Cooke and H. F. Haynes, *Aust. J. Chem.* **11**, 225 (1958).

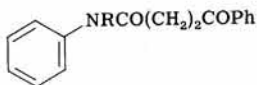
CO_2Me ; $\text{R}^4 = \text{R}^5 = \text{H}$) with sodium in toluene at 100° gives a mixture of **56** ($\text{R}^1 = \text{Me}$, Et; $\text{R}^2 = \text{CO}_2\text{Me}$; $\text{R}^3 = \text{OH}$; $\text{R}^4 = \text{H}$) and **55** ($\text{R}^1 = \text{Me}$, Et; $\text{R}^2 = \text{Me}$; $\text{R}^3 = \text{OH}$; $\text{R}^4 = \text{R}^5 = \text{H}$). Sodium methoxide, in place of sodium, increased the yield of the quinolone.⁴⁵ A combination of the Stobbe and Dieckmann condensations of ethyl anthranilate with diethyl succinate in the presence of sodium hydride gave **56** ($\text{R}^1 = \text{R}^4 = \text{H}$; $\text{R}^2 = \text{CO}_2\text{Et}$; $\text{R}^3 = \text{OH}$). The acid **56** ($\text{R}^1 = \text{R}^4 = \text{H}$; $\text{R}^2 = \text{CO}_2\text{H}$;



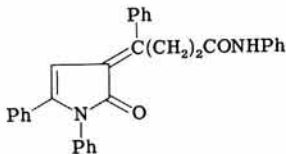
(56)

$\text{R}^3 = \text{OH}$) could not be decarboxylated.⁴⁶ Similar resistance to decarboxylation has been observed with a compound obtained by acid hydrolysis of **9** ($\text{R}^1 = \text{CO}_2\text{Me}$; $\text{R}^2 = \text{R}^3 = \text{H}$) and assumed to be **9** ($\text{R}^1 = \text{CO}_2\text{H}$; $\text{R}^2 = \text{R}^3 = \text{H}$). It has been shown that ring contraction (see Section III,A) takes place during the hydrolysis and the compound formed has the enolic structure of **55** ($\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{R}^5 = \text{H}$; $\text{R}^3 = \text{OH}$), which would explain the fact that it cannot easily be decarboxylated.⁴⁷ Loev *et al.*⁴⁸ have recently reported that the Stobbe condensation of 2-amino-5-chlorobenzophenone with diethyl succinate directly gave **55** ($\text{R}^1 = \text{R}^2 = \text{R}^5 = \text{H}$; $\text{R}^3 = \text{Ph}$; $\text{R}^4 = \text{Cl}$) and none of the desired **56** ($\text{R}^1 = \text{H}$; $\text{R}^2 = \text{CO}_2\text{H}$; $\text{R}^3 = \text{Ph}$; $\text{R}^4 = \text{Cl}$).

The previously described⁴⁹ ring closure of 3-benzoylpropioanilide (**57**, $\text{R} = \text{H}$) with ammonium chloride into **56** ($\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{H}$; $\text{R}^3 = \text{Ph}$) has been disputed⁴⁸ and it has been claimed that the reaction product is **58**.



(57)



(58)

⁴⁵ U. Hoerlein and W. Geiger, *Arch. Pharm. (Weinheim)* **304**, 167 (1971).

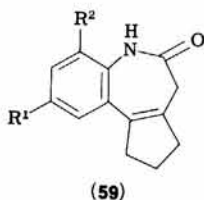
⁴⁶ H. B. MacPhillamy, R. L. Dziemian, R. A. Lucas, and M. E. Kuehne, *J. Amer. Chem. Soc.* **80**, 2172 (1958).

⁴⁷ T. A. Geissman and A. K. Cho, *J. Org. Chem.* **24**, 41 (1959).

⁴⁸ B. Loev, R. B. Greenwald, M. M. Goodman, and C. L. Zirkle, *J. Med. Chem.* **14**, 849 (1971).

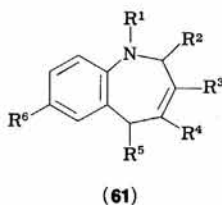
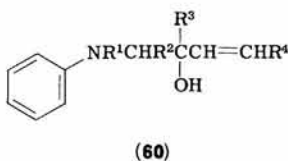
⁴⁹ A. Bertho, *Chem. Ber.* **90**, 29 (1957).

Low yields of **59** ($R^1, R^2 = H, Me$) were obtained by the condensation of the appropriate aniline with 2-cyclopentanone-1-acetic acid in acidic medium; similarly, aniline treated with levulinic, hippuric, and/or 2-

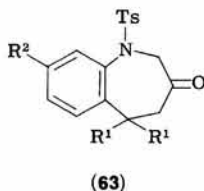
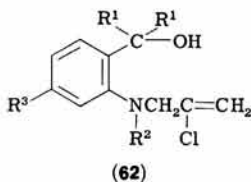


cyclohexanon-1-acetic acid gave **56** ($R^1 = R^2 = R^4 = H$; $R^3 = Me, Ph$).⁴⁹ An unsuccessful attempt was reported to cyclize **48** ($n = 3$; $R^1 = R^2 = R^4 = R^5 = H$; $R^3 = CO_2H$) with acetic anhydride-potassium acetate.^{43b}

The carbenium ion resulting from the allylic rearrangement of **60** ($R^1 = Me, Et$; $R^2 = H, Me$; $R^3 = Me, Et$; $R^4 = H, Me$) in diluted hydrochloric acid electrophilically attacks the benzene nucleus to give good yields of the appropriate **61** ($R^1, R^2, R^3, R^5 = H, Me, Et$; $R^4 = R^6 = H$).⁵⁰



The synthetic method for five- and six-membered rings developed by Lansbury⁵¹ has been applied⁵² to prepare seven-membered heterocyclics. The amino alcohol **62** ($R^1 = H, Me$; $R^2 = Ts$; $R^3 = H, Cl$) treated with 90% sulfuric acid at -5° afforded **63** ($R^1 = H, Me$; $R^2 = H, Cl$). Neither



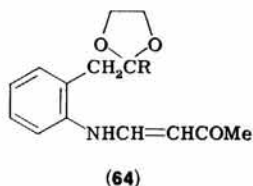
⁴⁹ R. Tiollais, A. Lattes, H. Bouget, T. Huet, and J. Bonnic, *C. R. Acad. Sci. Ser. C* **267**, 1350 (1968); J. Bonnic, J. Huet, A. Lattes, and H. Bouget, *ibid.* **272**, 672 (1971).

⁵¹ P. T. Lansbury and D. J. Scharf, *J. Amer. Chem. Soc.* **90**, 536 (1968).

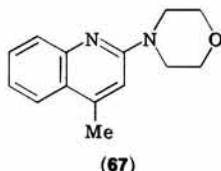
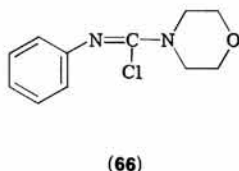
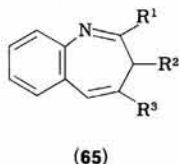
⁵² D. N. Gupta, I. McCall, A. McLean, and G. R. Proctor, *J. Chem. Soc. C*, 2191 (1970).

formic nor PPA were satisfactory for the reaction. The reaction proceeded only with *N*-protected amino alcohols; however, protecting groups other than tosyl gave unsatisfactory results.

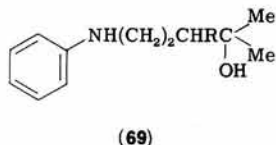
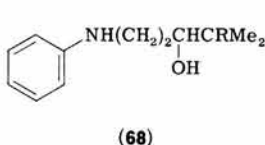
Heating the ketal **64** ($R = \text{Me, Et, iso-Pr, Bu}$) in aqueous alcohol in the presence of mineral acid gave high yields of **1** ($R^1\text{--}R^3 = \text{H}$; $R^4 = \text{Me}$; $R^5 = \text{COMe, COEt, COPr-iso, COBu}$).⁵³ An attempt to prepare **65**



($R^1 = \text{morpholino}$; $R^2 = R^3 = \text{H}$) by reacting the imidochloride **66** with propargylmagnesium bromide and, in turn, with PPA failed; only the lepidine **67** was obtained.⁵⁴



The cyclodehydration of the secondary alcohol **68** ($R = \text{H}$) with 70% perchloric acid gave a high yield of **7** ($R^1 = \text{H}$; $R^2 = \text{Me}$) in addition to **69** ($R = \text{H}$). Similarly, the alcohol **68** ($R = \text{Me}$) gave a high yield of

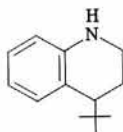


7 ($R^1 = R^2 = \text{Me}$) and traces of **69** ($R = \text{Me}$). The cyclization of **69** ($R = \text{H, Me}$) in this manner gave identical reaction products. The use of 60% perchloric acid for the cyclization of **68** ($R = \text{Me}$) gave rise to the quinoline **70** rather than the benzazepine **7** ($R^1 = R^2 = \text{Me}$). The reaction course is dependent on the acidity of the reaction medium, and

⁵³ H. J. Teuber and G. Emmerich, *Tetrahedron Lett.*, 4069 (1970).

⁵⁴ W. Ried and P. Weidemann, *Chem. Ber.* **104**, 3329 (1971).

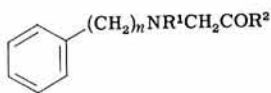
the alternative formation of the six- or seven-membered ring and simultaneous formation of the tertiary alcohols is explained on the basis of a carbenium ion formed from the secondary alcohols **68** ($R = H, Me$) undergoing ring closure, 1,2-hydride shift, methyl migration, and/or solvation.⁵⁵



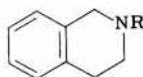
(70)

2. 2-Benzazepines

Although the Friedel-Crafts reaction failed to produce the seven-membered ring in the 1-benzazepine series, the method has been successfully used to prepare 2-benzazepines. The first study by von Braun *et al.*,⁵⁶ however, showed that the reaction carried out with *N*-(2-phenylethyl)-glycine chloride (**71**, $n = 2$; $R^1 = SO_2Ph$; $R^2 = Cl$) and aluminum chloride in nitrobenzene proceeded exothermically with evolution of carbon monoxide and hydrogen chloride to give **72** ($R = SO_2Ph$). Consequently,



(71)



(72)

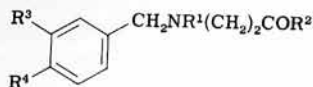
with the higher homolog **71** ($n = 3$; $R^1 = Ts$; $R^2 = Cl$) under the same conditions, **19** ($R^1 = H$; $R^2 = Ts$; $R^3-R^7 = H$) was obtained in 65% yield. 2-Benzazepines substituted in the aromatic ring by alkyl groups were prepared similarly.⁵⁷ The ring closure could also be achieved by merely refluxing **71** ($n = 3$; $R^1 = Ts$; $R^2 = OH$) with phosphorus pentoxide in xylene to give **19** ($R^1 = H$; $R^2 = Ts$; $R^3-R^7 = H$) in 80% yield.⁵⁸ On the other hand, when these reaction techniques were applied to cyclize the β -benzylaminopropionic acid or its chloride (**73**, $R^1 = CH_2Ph, SO_2Ph, Ts$; $R^2 = OH, Cl$; $R^3 = R^4 = H$) no cyclized product was obtained due

⁵⁵ B. D. Tilak, V. N. Gogte, and T. Ravindranathan, *Ind. J. Chem.* **7**, 24 (1969).

⁵⁶ J. von Braun, G. Blessing, and R. S. Cahn, *Chem. Ber.* **57**, 908 (1924).

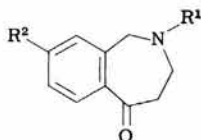
⁵⁷ J. von Braun and K. Wirz, *Chem. Ber.* **60**, 102 (1927).

⁵⁸ J. von Braun and O. Bayer, *Chem. Ber.* **60**, 1257 (1927).



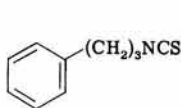
(73)

to excessive fragmentation of the starting material. Activation of the aromatic ring and the use of PPA as the catalyst also did not lead to the desired 2-benzazepin-5-one derivative.^{41a} Recently it has been shown that when the reaction, catalyzed with aluminum chloride, is carried out between -70° and $+20^{\circ}$, **73** ($R^1 = \text{Ts}$; $R^2 = \text{Cl}$; $R^3 = \text{OMe}$; $R^4 = \text{H}$) gives an 86% yield of **74** ($R^1 = \text{Ts}$; $R^2 = \text{OMe}$).⁵⁹ The Friedel-Crafts

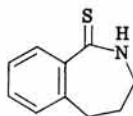


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intramolecular acylation of phenylalkylglycines has been studied with regard to the effect of temperature and amount of the catalyst on the reaction course⁶⁰ (see Section II,B, 3). The isothiocyanate **75** heated with



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(76)

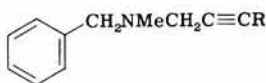
aluminum chloride afforded **76**.⁶¹ Aluminum chloride also catalyzed the ring closure of **77** ($R = \text{Ph}$) to **78**; PPA was not satisfactory. However, the same reaction carried out with the terminal acetylene **77** ($R = \text{H}$) gave only the isoquinoline **79**.^{62a} The ring closure of the acetylenes was previously described^{62b} to give compounds of different structure.

⁵⁹ I. MacDonald and R. G. Proctor, *J. Chem. Soc. C*, 1461 (1970).

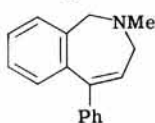
⁶⁰ J. Schlademan and R. Partch, *J. Chem. Soc. C*, 213 (1972).

⁶¹ Ger. Offen. 1,911,519; *Chem. Abstr.* **72**, 12601w (1970).

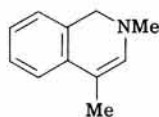
⁶² (a) J. R. Brooks and D. N. Harcourt, *J. Chem. Soc. C*, 625 (1969); British Patent 1,242,963; *Chem. Abstr.* **75**, 140718 (1971); (b) Japanese Patent 4489 (1964); *Chem. Abstr.* **61**, 5618h (1964).



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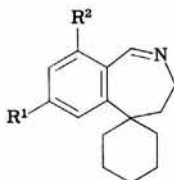


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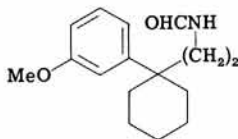


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Von Braun⁶ reported that no cyclization occurred when 3-phenylpropylamine was treated with formaldehyde dimethyl acetal. However, the Bischler-Napieralski cyclization was later successfully used to prepare 2-benzazepines. Thus, the spirobenzazepine **80** ($R^1 = \text{OMe}$; $R^2 = \text{H}$) was obtained by refluxing **81** with phosphorus pentoxide in benzene;

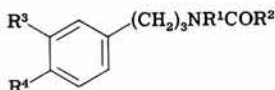


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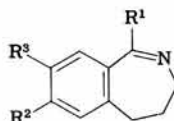


(81)

only traces of **80** ($R^1 = \text{H}$; $R^2 = \text{OMe}$) were formed. When PPA was used for the cyclization, a 1:1 mixture of both isomers was obtained.⁶³ Polyphosphoric esters were found⁶⁴ to be an efficient catalyst to cyclize **82** ($R^1 = \text{H}$; $R^2 = \text{H, Me, Ph}$; $R^3 = R^4 = \text{OMe}$) into **83** ($R^1 = \text{H, Me, Ph}$; $R^2 = R^3 = \text{OMe}$). The crude **83** ($R^1 - R^3 = \text{H}$), obtained from **82**

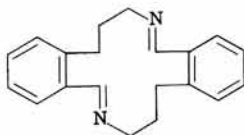


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(83)

($R^1 - R^4 = \text{H}$) using PPA-phosphorus pentoxide, was shown to dimerize to **84** on standing. The reverse transformation occurred in chloroform.



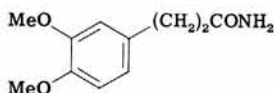
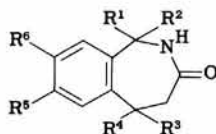
(84)

⁶³ M. Tomita and S. Minami, *Yakugaku Zasshi* **83**, 1022 (1963); *Chem. Abstr.* **60**, 7998c (1964).

⁶⁴ Y. Kanaoka, E. Sato, O. Yonemitsu, and Y. Ban, *Tetrahedron Lett.*, 2419 (1964).

The transformations are acid-catalyzed. It is suggested⁶⁵ that the previously⁶⁴ prepared compounds **83** ($R^1 = \text{H, Me, Ph}$; $R^2 = R^3 = \text{OMe}$) also exist as dimers. Various substituted 2-benzazepines, which are the subject of patents,⁶⁶⁻⁶⁸ were prepared by the Bischler-Napieralski reaction of *N*-acylated 3-phenylpropylamines using phosphorus pentoxide^{66, 67} and phosphorus oxychloride-phosphorus pentoxide.⁶⁸ The cyclization of *N*-formylated phenylalkylamines (**82**, $R^1 = \text{Me}$; $R^2 = \text{H}$; $R^3 = R^4 = \text{O}-\text{CH}_2-\text{O}$) with phosphorus oxychloride, designated as the Vilsmeier intramolecular reaction,⁶⁹ gave an 82% yield of **19** ($R^1 = \text{OH}$; $R^2 = \text{Me}$; $R^3 = R^4 = R^7 = \text{H}$; $R^5 = R^6 = \text{O}-\text{CH}_2-\text{O}$).

The Pictet-Spengler type cyclization has been carried out with **85**, which on treatment with benzaldehyde or 3,4-dimethoxybenzaldehyde and PPA in acetic acid gave **86** [$R^1 = \text{Ph, 3,4-(OMe)}_2\text{C}_6\text{H}_3$; $R^2 = R^3 = R^4 = \text{H}$; $R^5 = R^6 = \text{OMe}$] in good yields. However, the reaction did not proceed with aliphatic aldehydes. An alternative reaction of **85** with

**(85)****(86)**

s-trioxan and PPA-glacial acetic acid, or with paraldehyde and trifluoroacetic acid, gave **86** ($R^1-R^4 = \text{H}$; $R^5 = R^6 = \text{OMe}$). In this manner veratraldehyde with **82** ($R^1 = R^2 = \text{H}$; $R^3 = R^4 = \text{OMe}$) gave an 84% yield of **19** [$R^1 = 3,4\text{-(OMe)}_2\text{C}_6\text{H}_3$; $R^2 = \text{CHO}$; $R^3 = R^4 = R^7 = \text{H}$; $R^5 = R^6 = \text{OMe}$].⁷⁰

Phenol oxidative coupling of **87** ($R^1 = \text{Me}$; $R^2 = \text{OMe}$; $R^3 = \text{H}$) was reported^{71a} to give only very low yields of **88** ($R^1 = \text{Me}$; $R^2 = \text{OH}$; $R^3 = R^4 = \text{H}$); however, **87** ($R^1 = \text{SO}_2\text{Me}$; $R^2 = R^3 = \text{OMe}$) with alkaline ferricyanide afforded an 81% yield of **88** ($R^1 = \text{SO}_2\text{Me}$; $R^2 = \text{H}$; $R^3 = \text{OH}$; $R^4 = \text{OMe}$). When the coupling was carried out with **87**

⁶⁵ I. M. Goldman, J. K. Larson, J. R. Tretter, and E. G. Andrews, *J. Amer. Chem. Soc.* **91**, 4941 (1969).

⁶⁶ Japanese Patent 4488 (1964); *Chem. Abstr.* **61**, 5619g (1964).

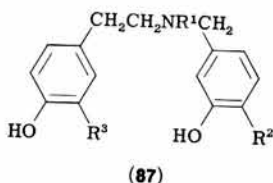
⁶⁷ U. S. Patent 3,409,607; *Chem. Abstr.* **70**, 77827c (1969).

⁶⁸ U. S. Patent 3,483,186; *Chem. Abstr.* **72**, 121383 (1970).

⁶⁹ F. Dallacker, D. Bernabei, R. Katzke, and P.-H. Benders, *Chem. Ber.* **104**, 2526 (1971).

⁷⁰ R. R. Wittekind and S. Lazarus, *J. Heterocycl. Chem.* **8**, 495 (1971).

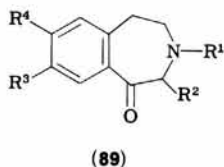
⁷¹ (a) D. H. R. Barton and G. W. Kirby, *J. Chem. Soc.*, 806 (1962); (b) R. A. Abramovitch and S. Takahashi, *Chem. Ind. (London)*, 1039 (1963).



($R^1 = H$; $R^2 = R^3 = OH$) no pure cyclized product was obtained.^{71b}

3. 3-Benzazepines

The initial attempts to cyclize phenylethylglycine chloride (**71**, $n = 2$; $R = SO_2Ph$, Ts; $R^2 = Cl$) into the corresponding 3-benzazepin-1-one with aluminum chloride failed,⁵⁶⁻⁵⁸ or only traces of **89** ($R^1 = Ts$; $R^2 = R^3 = R^4 = H$) were detected.^{41a} The cyclization of **71** ($n = 2$; $R^1 = Ts$;



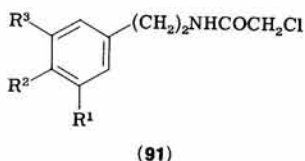
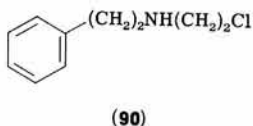
$R^2 = OH$) with PPA gave only **72** ($R = Ts$).^{41a} The reaction has received a detailed investigation,^{60, 72, 73} and it has been shown that the optimal reaction temperature for the formation of the seven-membered ring from the acid chloride and aluminum chloride is -10° and that the amount of the catalyst used determines whether a six- or seven-membered ring is formed.⁶⁰ The Friedel-Crafts intramolecular alkylation proceeded successfully with *N*-(2-chloroethyl)phenethylamines. Substituted propiophenones are used as the starting material for patented benzazepines; the usual reactions convert the former into styrenes which, in turn, react with sodium and ethylenimine to give, via *N*-(2-phenylethyl)aziridines, the appropriate **90** which on heating with aluminum chloride form the corresponding **35** having substituents both in the aromatic and heterocyclic ring.⁷⁴ Similarly, **91** ($R^1-R^3 = H$) gave **34** ($R^1-R^{10} = H$).⁷⁵

⁷² M. A. Rehman and G. R. Proctor, *J. Chem. Soc. C*, 58 (1967).

⁷³ Ger. Offen. 1,934,150; *Chem. Abstr.* **72**, 90331x (1970).

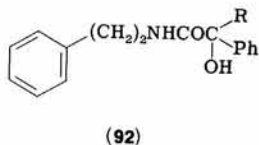
⁷⁴ Ger. Offen. 1,940,512; *Chem. Abstr.* **73**, 120526; Swiss Patent 500,194; *Chem. Abstr.* **74**, 141586 (1971); S. African Patent 6801,019; *Chem. Abstr.* **71**, 61251 (1969); S. African Patent 6804,879; *Chem. Abstr.* **72**, 90330w (1970); S. African Patent 6907,046; *Chem. Abstr.* **73**, 120521z (1970).

⁷⁵ M. D. Nair and P. A. Malik, *Indian J. Chem.* **5**, 169 (1967).



The photochemical cyclization of *N*-chloroacetylphenethylamines has been extensively studied by Witkop and co-workers. The irradiation of **91** ($R^1 = R^2 = H$; $R^3 = OH$) with a high-pressure mercury lamp results in the ring closure para to the hydroxy group to give **34** ($R^1-R^7 = H$; $R^8 = OH$; $R^9 = R^{10} = H$) in 70% yield. The corresponding iodoacetyl derivative gives only an 11% yield of the product. The cyclization ortho to the hydroxyl group occurs with **91** ($R^1 = OH$; $R^2 = R^3 = OMe$). The course of the photochemical ring closure is dependent on the nature and position of the substituent in the aromatic ring of the respective phenethylamine. Other compounds than 3-benzazepines are also formed. Their structures have been elucidated and a mechanism for the photo-cyclization proposed.⁷⁶⁻⁸²

Although it was possible to cyclodehydrate the benzilamide **92** ($R = Ph$) with concentrated sulfuric acid in acetic acid into **34** ($R^1 = R^2 = Ph$;



$R^3-R^{10} = H$) in 84% yield, an analogous reaction with the mandelic acid amide **92** ($R = H$) did not proceed.⁸³ Only when the phenethyl ring of the mandelic amide was activated with ethoxy groups was **34** ($R^1 = Ph$;

⁷⁶ O. Yonemitsu, T. Tokuyama, M. Chaykovsky, and B. Witkop, *J. Amer. Chem. Soc.* **90**, 776 (1968).

⁷⁷ O. Yonemitsu, Y. Okuno, Y. Kanaoka, I. L. Karle, and B. Witkop, *J. Amer. Chem. Soc.* **90**, 6522 (1968).

⁷⁸ O. Yonemitsu, H. Nakai, Y. Kanaoka, I. L. Karle, and B. Witkop, *J. Amer. Chem. Soc.* **91**, 4591 (1969).

⁷⁹ O. Yonemitsu, Y. Okuno, Y. Kanaoka, and B. Witkop, *J. Amer. Chem. Soc.* **92**, 5686 (1970).

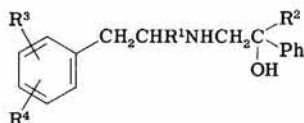
⁸⁰ O. Yonemitsu, H. Nakai, Y. Kanaoka, I. L. Karle, and B. Witkop, *J. Amer. Chem. Soc.* **92**, 5691 (1970).

⁸¹ T. Iwakuma, H. Nakai, O. Yonemitsu, D. S. Jones, I. L. Karle, and B. Witkop, *J. Amer. Chem. Soc.* **94**, 5136 (1972).

⁸² Y. Okuno, K. Hemmi, and O. Yonemitsu, *Chem. Pharm. Bull.* **20**, 1164 (1972).

⁸³ P. A. Petyunin, *Zh. Obshch. Khim.* **22**, 700 (1952); *Chem. Abstr.* **47**, 5385 (1953).

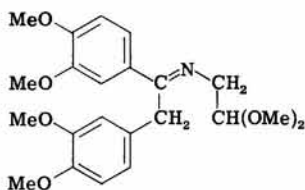
R^2 – R^7 = H; R^8 = R^9 = OEt; R^{10} = H) obtained using sulfuric acid. Better results were obtained with PPA or 100% phosphoric acid, and by using PPA it was also possible⁸⁴ to cyclize unactivated **92** (R = H). Substituted 1,2,4,5-tetrahydro-3*H*-3-benzazepines were prepared by cyclizing the appropriate tertiary alcohols (**93**, R^1 , R^2 = H, Me; R^3 ,



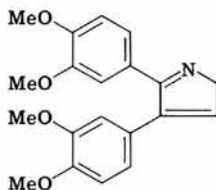
(93)

R^4 = H, OMe) with sulfuric acid.⁸⁵

The structure of a compound obtained from **94** with concentrated sulfuric acid has been the subject of discussion.^{86–88} The pyrrole **95** was suggested.⁸⁷

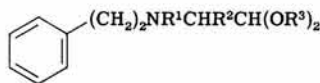


(94)



(95)

This was disputed by Battersby and Yeowell,⁸⁸ and finally Sainsbury *et al.*⁸⁹ showed by NMR that the correct structure was **46** [R^1 = H; R^2 = 3,4-(OMe)₂C₆H₃; R^3 = R^4 = OMe]. In a similar reaction, the acetal **96** (R^1 = H, Me; R^2 = H, Ph; R^3 = Me, Et) with boron trifluoride



(96)

in methylene chloride⁹⁰ gave **35** (R^1 = OMe, OEt; R^2 = H, Ph; R^3 = H,

⁸⁴ M. Hamon, *C. R. Acad. Sci. Ser. C* **255**, 1619 (1962).

⁸⁵ U. S. Patent 3,393,192; *Chem. Abstr.* **69**, 96507 (1968). British Patent 1,118,688; *Chem. Abstr.* **69**, 106576 (1968).

⁸⁶ P. Fritsch, *Ann. Chem.* **329**, 37 (1903).

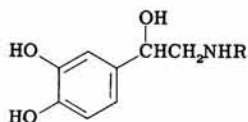
⁸⁷ D. A. Guthrie, A. W. Frank, and C. B. Purves, *Can. J. Chem.* **33**, 729 (1955).

⁸⁸ A. R. Battersby and D. A. Yeowell, *J. Chem. Soc.*, 1888 (1958).

⁸⁹ M. Sainsbury, D. W. Brown, S. F. Dyke, and G. Hardy, *Tetrahedron* **25**, 1881 (1969).

⁹⁰ J. Likforman and J. Gardent, *C. R. Acad. Sci. Ser. C* **268**, 2340 (1969).

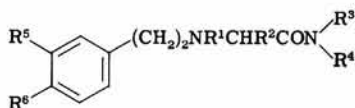
Me; $R^4-R^8 = H$). The condensation of the catecholamines **97** ($R = H$,



(97)

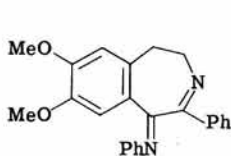
Me, iso-Pr) with hydrated glyoxylic acid under physiological conditions gave good yields of **34** ($R^1 = R^5 = R^8 = R^9 = OH$; $R^3 = H$, Me, iso-Pr; $R^2 = R^4 = R^6 = R^7 = R^{10} = H$).^{91,92}

Phosphorus oxychloride containing 5% of water catalyzed the ring closure of **98** ($R^1 = Ms$, Ts, SO_2CH_2Ph ; $R^2 = R^3 = H$; $R^4 = Ph$;

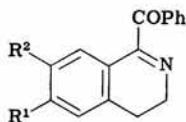


(98)

$R^5 = R^6 = OMe$, OEt) to give **89** ($R^1 = Ms$, Ts, SO_2CH_2Ph ; $R^2 = H$; $R^3 = R^4 = OMe$, OEt). It was not possible to cyclize aromatic-unsubstituted *N,N*-disubstituted amides or *N,N*-unsubstituted amides in this manner.^{93,94} It has, however, been reported⁹⁵ that when **98** ($R^1 = Ts$; $R^2 = Ph$; $R^3 = H$; $R^4 = Ph$; $R^5 = R^6 = OMe$) is reacted as above, **99** is obtained which, upon hydrolysis, affords only the isoquinoline **100** ($R^1 = R^2 = OMe$).



(99)



(100)

An aldol-like condensation of phthalaldehyde (**101**) with iminodiacetic

⁹¹ J. P. Fourneau, C. Gaignault, R. Jacquier, O. Stoven, and M. Davy, *Chim. Ther.* **4**, 67 (1969).

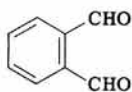
⁹² Ger. Offen. 1,944,121; *Chem. Abstr.* **72**, 111311h (1970).

⁹³ G. Hazebroucq and J. Gardent, *C. R. Acad. Sci. Ser. C* **257**, 923 (1963).

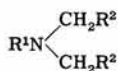
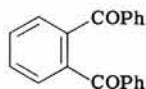
⁹⁴ G. Hazebroucq, *Ann. Chim. (Paris)* [14] **1**, 221 (1966).

⁹⁵ Y. Inubushi, T. Harayama, and K. Takeshima, *Chem. Pharm. Bull.* **20**, 689 (1972).

acid esters (**102**, $R^1 = \text{Me, Ph}$; $R^2 = \text{CO}_2\text{Me, CO}_2\text{Et}$) catalyzed with



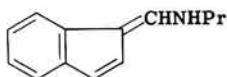
(101)

(102); $R = \text{H}$ 

(103)

sodium or potassium in methanol,^{96a,97} or potassium *t*-butoxide^{96b} gave low yields of **3** ($R^1 = R^5 = \text{H}$; $R^2 = R^4 = \text{CO}_2\text{Me, CO}_2\text{Et}$; $R^3 = \text{Me, Ph}$). The iminodiacetonitrile (**102**, $R^1 = \text{Me, R}^2 = \text{CN}$) reacted similarly, while *N*-aryl-substituted **102** ($R^1 = \text{Ar}$; $R^2 = \text{CN}$) underwent further reactions of the cyano groups, i.e., hydrolysis and esterification. The diketone **103** gave an azepine only with **102** ($R^1 = \text{iso-Pr}$; $R^2 = \text{CN}$), while other *N*-substituted **102** ($R^1 = \text{Et, Pr, C}_6\text{H}_{11}$, 4- $\text{C}_6\text{H}_4\text{Me}$; $R^2 = \text{CN}$) gave only open-chain condensation products.⁹⁸

An attempt to employ the Paal-Knorr synthesis of pyrrole to prepare 3-benzazepines failed. For example, **40** ($R = \text{CHO}$) treated with *n*-propylamine gave the benzofulvene **104**.⁹⁹



(104)

The Dieckmann condensation of dimethyl phthalate with **102** ($R^1 = \text{Me, Et, Ph}$; $R^2 = \text{CO}_2\text{Me, CO}_2\text{H}$) was reported¹⁰⁰ to give low yields of **3** ($R^1 = R^5 = \text{OH}$; $R^2 = R^4 = \text{CO}_2\text{Me, CO}_2\text{H}$; $R^3 = \text{Me, Et, Ph}$).

C. BECKMANN REARRANGEMENT

The Beckmann rearrangement of bicyclic ketone oximes to give seven-membered lactams is simple to carry out, usually gives high yields of the reaction products, and the starting materials are easily accessible. However, side reactions, most notably the Semmler-Wolff aromatization, fragmentation, and ring contraction, make the rearrangement less attractive. A

⁹⁶ (a) K. Dimroth and H. Freyschlag, *Angew. Chem.* **68**, 518 (1956); *Chem. Ber.* **89**, 2602 (1956); (b) *ibid.* **90**, 1628 (1957).

⁹⁷ F. Dallacker, K. W. Glombitza, and M. Lipp, *Ann. Chem.* **643**, 82 (1961).

⁹⁸ K. Dimroth, D. Holzner, and H. G. Aurich, *Chem. Ber.* **98**, 3907 (1965).

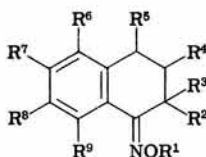
⁹⁹ R. Huisgen, E. Laschtuvka, I. Ugi, and A. Kammermeier, *Ann. Chem.* **630**, 128 (1960).

¹⁰⁰ W. E. Hahn, J. Epszajn, and Z. Madeja-Kotkowska, *Rocz. Chem.* **39**, 1423 (1965); *Chem. Abstr.* **64**, 17540 (1966).

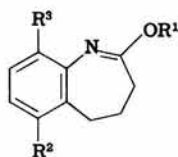
mixture of reaction products can be formed due to concurrent alkyl and aryl migration which is greatly influenced by substituents in the starting oxime. Interesting conclusions have emerged from the studies on the Beckmann rearrangement of substituted 1- and 2-tetralone oximes. The reaction might in certain cases be nonstereospecific and the lactam formation may proceed via a new reaction mechanism involving ring scission of the cyclic ketone oxime and Ritter-type recyclization.

1. 1-Benzazepines

Schroeter *et al.*⁵ showed that *O*-acetyl tetralone oximes substituted in the position ortho to the oxime group, i.e., **105** ($R^1 = \text{Ac}$; $R^2-R^5 = \text{H}$; $R^6 = R^9 = \text{Me}$; $R^7 = R^8 = \text{H}$) underwent the normal Beckmann rearrangement when treated with acetic acid-acetic anhydride-hydrogen chloride mixture (Beckmann mixture) to give **5** ($R^1-R^4 = \text{H}$; $R^5 = R^8 = \text{Me}$; $R^6 = R^7 = \text{H}$). However, 1-tetralones substituted in the aromatic ring at various positions other than ortho to the oxime group, with either electron-releasing or electron-withdrawing groups, underwent the Semmler-Wolff aromatization to give the appropriate naphthylamines. On the other hand, it was possible to rearrange *O*-arylsulfonated 1-tetralone oxime **105** ($R^1 = \text{Ts}$; $R^2-R^9 = \text{H}$) into **106** ($R^1 = \text{Ph}$; $R^2 = R^3 = \text{H}$)



(105)



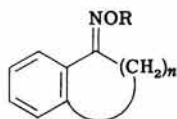
(106)

on heating with phenol, while the reaction in methanol or ethanol afforded only the ring-cleavage products **4** ($R^1 = \text{Me, Et}$; $R^2 = \text{H}$). When the aromatic ring of 1-tetralone was deactivated with various substituents, no reaction occurred with *O*-arylsulfonyl oximes, while the *O*-acetyl derivatives gave the corresponding α -naphthylamines. These differences in the reaction course were explained on steric grounds and on the basis of the different acidities of acetic and *p*-toluenesulfonic acid.⁵ Since then, the mechanism of the Semmler-Wolff aromatization has been formulated by Vorozhtsov and Koptiug,¹⁰¹ who did not observe the formation of lactams among the various reaction products of the rearrangement of 1-tetralone oxime. Nor did Nizamuddin and Chaudhury, who attempted

¹⁰¹ N. N. Vorozhtsov and V. A. Koptiug, *J. Gen. Chem. USSR* **28**, 1697 (1958); *Chem. Abstr.* **53**, 302 (1959).

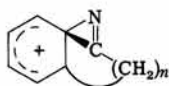
to rearrange **105** ($R^1-R^7 = H$; $R^8 = OMe$; $R^9 = H$) with the Beckmann mixture but obtained only 7-methoxy-1-naphthylamine.¹⁰² Bauer and Hewitson,¹⁰³ while accepting the reaction mechanism of Vorozhtsov,¹⁰¹ did isolate a lactam from the rearrangement of a 1-tetralone oxime using the Beckmann mixture; however, the lactam turned out to be a derivative of 2-benzazepin-1-one (see Section II,C, 2). Heating **105** ($R^1 = SO_2Ph$; $R^2-R^9 = H$) with aqueous potassium acetate¹⁰⁴ gave a 64% yield of **5** ($R^1-R^8 = H$).

Huisgen and co-workers studied the kinetics of the Beckmann rearrangement of *O*-acylated benzocycloalkane oximes (**107**) [$n = 2-5$; $R = SO_2Ph$,



(107)

2,4,6-(NO_2)₃C₆H₂] and concluded that the reaction rate is dependent on the alicyclic ring size, the reactivity being in the order $5 \ll 6 < 7 < 8$, as well as on the configuration of the oxime group. The aryl migration is preferred and the rearrangement proceeds via the cation **108** ($n = 2-5$) (slow, rate-determining step) whose ring cleavage (fast step) would be enhanced by the presence of nucleophilic reagents and by the extent of ring strain. The formation of the phenonium-like cation suggests that the reaction will be affected by activating or deactivating substituents in the



(108)

aromatic ring, and that the aryl migration is, in fact, an electrophilic substitution on the migrating benzene ring.¹⁰⁴⁻¹⁰⁶ Horning *et al.*^{107,108} introduced polyphosphoric acid (PPA) as the reagent for the Beckmann rearrangement of bicyclic oximes. At first it appeared that this reagent

¹⁰² S. Nizamuddin and D. N. Chaudhury, *J. Indian Chem. Soc.* **40**, 960 (1963).

¹⁰³ L. Bauer and R. E. Hewitson, *J. Org. Chem.* **27**, 3982 (1962).

¹⁰⁴ R. Huisgen, I. Ugi, H. Brade, and E. Rauenbusch, *Ann. Chem.* **586**, 30 (1954).

¹⁰⁵ R. Huisgen, J. Witte, H. Walz, and W. Jira, *Ann. Chem.* **604**, 191 (1957).

¹⁰⁶ R. Huisgen, J. Witte, and I. Ugi, *Chem. Ber.* **90**, 1844 (1957).

¹⁰⁷ E. C. Horning, V. L. Stromberg, and H. A. Lloyd, *J. Amer. Chem. Soc.* **74**, 5153 (1952).

¹⁰⁸ H. A. Lloyd, L. U. Matternas, and E. C. Horning, *J. Amer. Chem. Soc.* **77**, 5932 (1955).

would suppress the side reactions and improve the yields. Thus, **105** ($R^1-R^9 = H$) heated with PPA at 130° for 10 minutes gave a 91% yield of **5** ($R^1-R^8 = H$). However, later it was shown⁹ that rearrangement to an indole occurred on heating **105** ($R^1-R^4 = H$; $R^5 = CO_2H$, $R^6-R^9 = H$) with PPA, to give **14**, and only a low yield of **5** ($R^1 = R^2 = H$; $R^3 = CO_2Me$; $R^4-R^8 = H$) was obtained by the rearrangement of **105** ($R^1-R^3 = H$; $R^4 = CO_2Me$; $R^5-R^9 = H$), suggesting that rearrangement to an indole or quinoline (see Section III,A) might occur, although none of these was isolated.¹⁰⁸ Similar rearrangements of the benzazepine ring to an indole and quinoline have been observed.¹⁰⁹

Other examples of the use of PPA can be found^{102,103,110}; variously substituted 1-tetralones (**105**, all R 's = H unless indicated: $R^8 = OMe$,^{102,111} Me ,¹¹¹ Et ,¹¹¹ NO_2 ,¹¹¹ $R^7 = R^8 = Me$,¹¹² $R^7 = OMe$,¹¹³ $R^6 = Et$, $R^8 = iso-Pr$ ¹¹⁴) gave the appropriate 1-benzazepin-2-ones. It has been claimed that PPA induces exclusively the aryl migration, while the use of Beckmann mixture results in preferential alkyl migration.¹⁰³ The steric effect of substituents on the course of the rearrangement, using PPA, has been studied by Conley and Frainier¹¹⁵ and Lansbury and Mancuso.¹¹⁶ α,α -Disubstituted 1-tetralone oximes [**105**, $R^1 = H$, $R^2 = R^3 = Me$, $-(CH_2)_5-$; $R^4-R^9 = H$] afforded almost quantitatively a single lactam on heating with PPA, i.e., **5** [$R^1 = R^2 = Me$, $-(CH_2)_5-$; $R^3-R^8 = H$] as a result of phenyl migration despite the steric hindrance at the α -carbon of the oxime. Little fragmentation of the oxime to nitrile was observed. It is postulated that the steric control of the rearrangement due to oxime configuration is not favored in this case where steric crowding in either configuration of the oxime exists. Rather, the dissociation of the oximino hydroxyl group would give a nonstereoselective, positively charged nitrogen ion, and group migration would be controlled, as in carbon-carbon rearrangements, by migratory aptitude due primarily to the transition-state stabilization. The previously suggested¹⁰⁵ bridged ion **108** ($n = 3$) conforms to these conclusions.¹¹⁵

The *t*-butyl group in **105** ($R^1-R^5 = H$; $R^6 = Br$; $R^7 = R^8 = H$; $R^9 = t-Bu$) was split off during the rearrangement to give a 100% yield of

¹⁰⁹ G. N. Walker, D. Alkalay, and R. T. Smith, *J. Org. Chem.* **30**, 2973 (1965).

¹¹⁰ U. S. Patent 2,991,286; *Chem. Abstr.* **56**, 3466 (1962).

¹¹¹ French Patent 1,473,839; *Chem. Abstr.* **68**, 78164e (1968).

¹¹² A. H. Rees and K. Simon, *Can. J. Chem.* **47**, 1227 (1969).

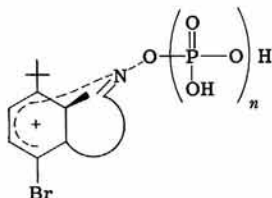
¹¹³ R. Futaki, *Tetrahedron Lett.*, 2455 (1967).

¹¹⁴ G. M. Strunz, *Tetrahedron* **24**, 2645 (1968).

¹¹⁵ R. T. Conley and L. J. Frainier, *J. Org. Chem.* **27**, 3844 (1962).

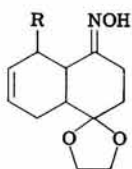
¹¹⁶ P. T. Lansbury and N. R. Mancuso, *Tetrahedron Lett.*, 2445 (1965); *J. Amer. Chem. Soc.* **88**, 1205 (1966).

5 ($R^1-R^4 = H$; $R^5 = Br$; $R^6-R^8 = H$). No oxime-insertion products were formed, contrary to the behavior of indanones. This is due to the flexibility of the tetralone system, which rearranges with aryl-assisted ionization of the oxime polyphosphate **109** without forming a discrete

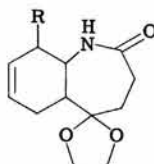


(109)

immonium cation. Aryl migration is more favorable energetically due to less torsional strain in the transition state and such participation outweighs the steric hindrance.¹¹⁶ Vogel *et al.*¹¹⁷ and others¹¹⁸ reported that both 1- and 2-benzazepinones were formed in varying ratios in the rearrangement of aromatic substituted 1-tetralones with PPA. Thus, **105** ($R^1-R^3 = H$; $R^4 = CO_2Et$; $R^5 = Ph$; $R^6-R^9 = H$) exclusively gave the appropriate 1-benzazepin-2-one, while **105** ($R^1-R^3 = H$; $R^4 = CO_2Et$; $R^5 = 3,4-(OMe)_2C_6H_3$; $R^6 = R^9 = H$; $R^7 = R^8 = OMe$) gave a mixture of both the corresponding 1- and 2-benzazepinones. Tosyl chloride in pyridine was used for the rearrangement of the oximes **110** ($R = H, Et$) to give high yields of **111** ($R = H, Et$).^{119,120} Fragmentation in the Beck-



(110)



(111)

mann rearrangement of decalone-1,5-diones has been studied by Eisele *et al.* The absence or low concentration of base does not interfere with the normal course of the rearrangement, but higher concentrations induce fragmentation. Thus, heating **112** ($R = H$) in 80% ethanol gave a high

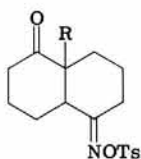
¹¹⁷ A. Vogel, F. Troxler, and A. Lindenmann, *Helv. Chim. Acta* **52**, 1929 (1969).

¹¹⁸ Japanese Patent 7114,658; *Chem. Abstr.* **75**, 48937m (1971).

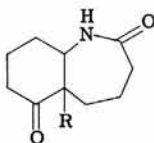
¹¹⁹ U. S. Patent 3,294,817; *Chem. Abstr.* **67**, 90787 (1967).

¹²⁰ S. I. Sallay, *J. Amer. Chem. Soc.* **89**, 6762 (1967).

yield of **113** ($R = H$), while a seven-center fragmentation occurred on



(112)

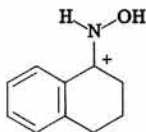


(113)

carrying out the reaction in the presence of sodium hydroxide or methoxide or potassium *t*-butoxide. However, the fragmentation was almost completely suppressed when the γ -position to the oxime group was substituted with dialkylamino groups.¹²¹⁻¹²⁴

2. 2-Benzazepines

Contrary to the findings of Schroeter *et al.*⁵ that the Beckmann rearrangement does occur with certain 1-tetralone oximes, Vorozhtsov¹⁰¹ and Nizamuddin¹⁰² claim that no formation of lactam takes place. Bauer and Hewitson,¹⁰³ however, did isolate **18** [$R^1 = 2$ -(4-pyridyl)ethyl, 2-(2-pyridyl)ethyl; $R^2 = H$] in addition to 2-chloro-2-[2-(4-pyridyl)ethyl]-1-tetralone and 2-[2-(4-pyridyl)ethyl]-1-naphthylamine, when **105** [$R^1 = H$, $R^2 = 2$ -(4-pyridyl)ethyl, 2-(2-pyridyl)ethyl; R^3 - $R^9 = H$] was treated with the Beckmann mixture. These authors claimed that this reagent gave exclusively the 2-benzazepin-1-one derivatives, while PPA resulted only in the corresponding 1-benzazepin-2-ones. A reaction mechanism has been proposed involving either the isomerization of the oxime via **114** to the *syn*-aryl configuration favoring alkyl migration or the formation



(114)

of the aziridine intermediates **115** \leftrightarrow **116** which undergo nucleophilic

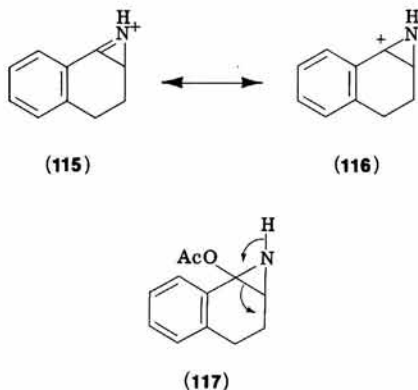
¹²¹ C. A. Grob, W. Eisele, and E. Renk, *Angew. Chem.* **76**, 106 (1964).

¹²² W. Eisele, C. A. Grob, and E. Renk, *Tetrahedron Lett.*, 75 (1963).

¹²³ W. Eisele, C. A. Grob, E. Renk, and H. von Tschammer, *Helv. Chim. Acta* **51**, 816 (1968).

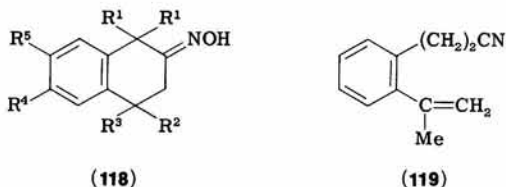
¹²⁴ K. G. Artz and C. A. Grob, *Helv. Chim. Acta* **51**, 807 (1968).

attack by the acetate ion to give **117**, which then collapses into **83** ($R^1 =$



OAc; $R^2 = R^3 = H$) followed by hydrolysis to give the lactam.

On the other hand, Evans and Lockhart¹²⁵ reported that treating **105** ($R^1-R^6 = H$; $R^7 = OMe$; $R^8 = R^9 = H$) with PPA gave **18** ($R^1 = H$; $R^2 = OMe$) as the major product and only "some" 1-benzazepin-2-one. The use of sulfuric acid resulted in tarry products. The 2-tetralone oxime (**118**, $R^1 = R^2 = R^3 = Me$; $R^4 = R^5 = H$) was reported¹²⁶ to give 24% yield of **86** ($R^1-R^4 = Me$; $R^5 = R^6 = H$). Since then, Conley and Lange¹²⁷ have studied 2-tetralone oximes and shown another mechanism by which the products of "Beckmann rearrangement" were formed. When the oxime **118** ($R^1 = Me$; $R^2-R^5 = H$) was treated with phosphorus pentachloride, a 93-96% yield of the nitrile **119** was obtained. The nitrile could

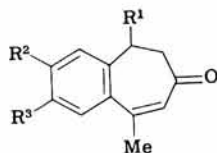


be converted by heating with PPA into **86** ($R^1 = R^2 = Me$; $R^3-R^6 = H$). When hot PPA was used for the rearrangement of oxime **118**, **86** ($R^1 = R^2 = Me$; $R^3-R^6 = H$) in 24% yield and the enone **120** ($R^1 = R^2 = R^3 = H$) in 71% yield, respectively, were isolated. Other oximes [**118**, $R^1 =$

¹²⁵ D. Evans and I. M. Lockhart, *J. Chem. Soc.*, 4806 (1965).

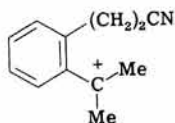
¹²⁶ H. A. Bruson, F. W. Grant, and E. Bobko, *J. Amer. Chem. Soc.* **80**, 3633 (1958).

¹²⁷ R. T. Conley and R. J. Lange, *J. Org. Chem.* **28**, 210 (1963).



(120)

$R^2 = R^3 = \text{Me}$; $R^4 = R^5 = \text{H}$; and **118**, $R^1 = (\text{CH}_2)_5$; $R^2-R^5 = \text{H}$] reacted similarly. A mechanism has been suggested in which the intermediate carbenium ion **121** is formed by the fragmentation of the oxime,



(121)

and in turn, undergoes either an intramolecular Hoesch reaction to give the cyclic ketones or a Ritter reaction to give the lactams.¹²⁷ In agreement with these postulations, it has been shown¹²⁸ that when an electron-releasing substituent is in the position para to the electron-deficient carbon in **121**, the Ritter pathway does not take place and no lactam is formed. The Hoesch pathway, on the other hand, proceeds undisturbed to give the cyclic ketone. A substituent in the meta position does not effect the Ritter reaction and the appropriate lactam is formed. Thus, **118** ($R^1 = R^2 = \text{Me}$; $R^3 = R^4 = \text{H}$; $R^5 = \text{OMe}$) afforded **86** ($R^1 = R^2 = R^3 = \text{Me}$; $R^4 = R^5 = \text{H}$; $R^6 = \text{OMe}$) and **120** ($R^1 = \text{Me}$; $R^2 = \text{H}$; $R^3 = \text{OMe}$) in about equal amounts, while **118** ($R^1 = R^2 = \text{Me}$; $R^3 = R^5 = \text{H}$; $R^4 = \text{OMe}$) gave only the ketone **120** ($R^1 = \text{Me}$; $R^2 = \text{OMe}$; $R^3 = \text{H}$).

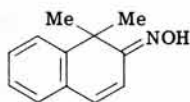
3. 3-Benzazepines

There are two reports in the literature of the Beckmann rearrangement to obtain 3-benzazepin-2-one. The *O*-tosyl derivative of **118** ($R^1-R^5 = \text{H}$) was heated in methanol at 100° in a sealed tube to give **34** ($R^1-R^{10} = \text{H}$) in 78% yield.¹²⁹ Irradiation of **122** with a high-pressure mercury lamp gave a low yield of **123** via **124**.¹³⁰

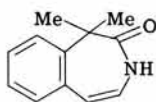
¹²⁸ P. C. Mukharji, D. Bhattacharjee, and T. K. Das Gupta, *Indian J. Chem.* **8**, 318 (1970).

¹²⁹ I. L. Knunyants and B. P. Fabrichnyi, *Dokl. Akad. Nauk SSSR* **68**, 523 (1949); *Chem. Abstr.* **44**, 1469 (1950).

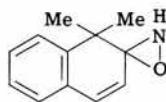
¹³⁰ T. Oine and T. Mukai, *Tetrahedron Lett.*, 157 (1969).



(122)



(123)



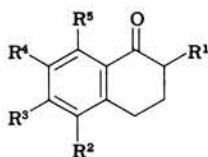
(124)

D. SCHMIDT REARRANGEMENT

The shortcomings of the Beckmann rearrangement at nitrogen as a method to synthesize the isomeric benzazepinones discussed above apply also to the Schmidt method. In this case, another side reaction, the formation of tetrazoles, may occur. The acidic medium used for the rearrangement plays a decisive role in directing the course of the reaction. The rearrangement may in some cases be nonstereospecific.

1. 1-Benzazepines

Briggs and De Ath¹³¹ were the first to react **125** ($R^1-R^5 = H$) with hydrogen azide in chloroform, using concentrated sulfuric acid as the



(125)

catalyst, to obtain a 70% yield of **5** ($R^1-R^8 = H$). Hydrogen azide was soon replaced by sodium azide and chloroform by acetic acid, but concentrated sulfuric acid was the reagent for the rearrangement of 1-tetralone^{104, 132} or variously substituted 1-tetralones.¹³³⁻¹³⁶ The postulation put forward^{104, 116, 132} for the mechanism and course of the Beckmann rearrangement (see Section II,C) applies for the Schmidt reaction as well. Smith¹³⁷ reported trichloroacetic acid to be an efficient catalyst-solvent to convert 1-tetralone into **5** ($R^1-R^8 = H$) in 85% yield, while hydrochloric acid was not a strong enough catalyst. Sulfuric acid decreased the yield. The

¹³¹ L. H. Briggs and G. C. De Ath, *J. Chem. Soc.*, 456 (1937).

¹³² R. Huisgen and I. Ugi, *Ann. Chem.* **610**, 57 (1957).

¹³³ Netherlands Appl. 6,516,320; *Chem. Abstr.* **65**, 15354 (1966).

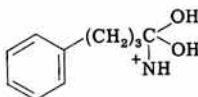
¹³⁴ U. S. Patent 3,312,691; *Chem. Abstr.* **68**, 49473z (1968).

¹³⁵ U. S. Patent 3,330,823; *Chem. Abstr.* **68**, 95713a (1968).

¹³⁶ J. M. Khanna and N. Anand, *J. Med. Chem.* **10**, 944 (1967).

¹³⁷ P. A. S. Smith, *J. Amer. Chem. Soc.* **70**, 320 (1948).

least strongly acid medium which will catalyze the reaction in a reasonable time gives the purest products in optimal yields. Trichloroacetic acid was subsequently used¹³⁸ to rearrange **125** ($R^1 = R^3 = R^5 = H$; $R^2 = R^4 = Et$) into **5** ($R^1-R^4 = H$; $R^5 = R^7 = Et$; $R^6 = R^8 = H$). Conley¹³⁹ employed polyphosphoric acid (PPA) as the catalyst-solvent to obtain a 90% yield of **5** ($R^1-R^8 = H$) from 1-tetralone. Methanesulfonic acid catalyzed the rearrangement of **125** ($R^1 = R^2 = R^3 = R^5 = H$; $R^4 = OH$) and **125** ($R^1 = R^2 = R^3 = H$; $R^4 = OH$; $R^5 = NO_2$) into **5** ($R^1-R^6 = H$; $R^7 = OH$; $R^8 = H$) and **5** ($R^1-R^6 = H$; $R^7 = OH$; $R^8 = NO_2$), respectively. Trifluoroacetic, trichloroacetic, and sulfuric acid were not satisfactory;¹⁴⁰ **125** ($R^1-R^3 = H$; $R^4 = NO_2$; $R^5 = H$) gave **5** ($R^1-R^6 = H$, $R^7 = NO_2$; $R^8 = H$), which was previously¹⁴¹ claimed to be prepared by direct nitration of **5** ($R^1-R^8 = H$). The structure for this nitration product is now suggested¹⁴⁰ to be **5** ($R^1-R^5 = H$, $R^6 = NO_2$, $R^7 = R^8 = H$). One report has appeared that γ -phenylbutyric acid with sodium azide in concentrated sulfuric acid or PPA directly gave **5** ($R^1-R^8 = H$). It has been concluded that the reaction proceeds via the cation **126**, which electrophilically attacks the benzene ring. The alternative mechanism whereby the butyric



(126)

acid first undergoes ring closure to give 1-tetralone followed by the normal Schmidt reaction has been excluded.¹⁴²

The electronic effect of a variety of substituents in the aromatic ring in the position para to the carbonyl group of 1-tetralones on the direction of the Schmidt rearrangement has been studied by Uyeo and co-workers^{143, 144a-c} with the use of sulfuric, and trichloroacetic acid, and

¹³⁸ T. Shingu, Y. Tsuda, S. Uyeo, Y. Yamato, and H. Harada, *Chem. Ind. (London)*, 1191 (1962).

¹³⁹ R. T. Conley, *Chem. Ind. (London)*, 438 (1958); *J. Org. Chem.* **23**, 1330 (1958).

¹⁴⁰ P. A. S. Smith and W. L. Berry, *J. Org. Chem.* **26**, 27 (1961).

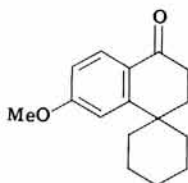
¹⁴¹ J. von Braun and M. Rawicz, *Chem. Ber.* **49**, 799 (1916).

¹⁴² S. K. Datta, C. Grundmann, and N. K. Bhattacharya, *J. Chem. Soc. C*, 2058 (1970).

¹⁴³ S. Minami, M. Tomita, H. Takamatsu, and S. Uyeo, *Chem. Pharm. Bull.* **13**, 1084 (1965).

¹⁴⁴ (a) M. Tomita, S. Minami, and S. Uyeo, *J. Chem. Soc. C*, 183 (1969); (b) N. Hazama, H. Irie, T. Mizutani, T. Shingu, M. Takada, and S. Uyeo, *ibid.*, 2947 (1968); (c) Y. Misaka, T. Mizutani, M. Sekido, and S. Uyeo, *ibid.*, 2954 (1968); *Chem. Commun.*, 1258 (1967).

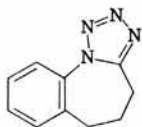
PPA as the catalysts. The ratio of products due to alkyl or aryl migration is affected by the substituents and the strength of the catalyst in favor of aryl-migration products, due to the increased conformational flexibility of the six-membered alicyclic ring as compared with the rigidity of the five-membered rings. However, no quantitative conclusions could be drawn. Only very strongly electron-releasing substituents, like methoxy or hydroxy, direct toward preferential alkyl migration. Sulfuric acid and PPA did not effect the ratio of migration products, while trichloroacetic acid increased the alkyl migration. Substituents in the aromatic ring of 1-tetralone in the position meta to the carbonyl tend to increase aryl migration. However, **127** rearranged to give a mixture of 1- and



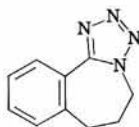
(127)

2-benzazepinones in about equal amount.^{144a} Evans and Lockhart report that the effect of aromatic substituents with an ether bond is in the direction of alkyl migration but can be reversed by other substituents in the alicyclic ring. Thus, **125** ($R^1 = \text{CH}_2\text{NMe}_2$; $R^2 = R^4 = R^5 = \text{H}$; $R^3 = \text{OMe}$) gave exclusively **5** ($R^1 = \text{CH}_2\text{NMe}_2$; $R^2\text{--}R^5 = \text{H}$; $R^6 = \text{OMe}$; $R^7 = R^8 = \text{H}$). Substituents in the peri position to the carbonyl did not affect the migration electronically; **125** ($R^1 = R^3 = R^4 = \text{H}$; $R^2 = R^5 = \text{Me}$) gave **5** ($R^1\text{--}R^4 = \text{H}$; $R^5 = R^8 = \text{Me}$; $R^6 = R^7 = \text{H}$) due to steric effects.¹²⁵ Other authors reported the formation of a mixture of isomeric benzazepines in the Schmidt rearrangement.^{117, 145, 146}

Huisgen *et al.*^{104, 132} predicted that the formation of the tetrazole **128** from tetralones would not be preferred to lactam formation using sulfuric



(128)



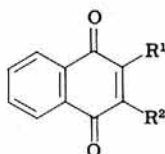
(129)

¹⁴⁵ L. H. Werner, S. Ricca, A. Rossi, and G. De Stevens, *J. Med. Chem.* **10**, 575 (1967).

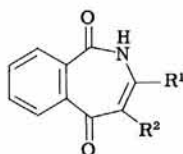
¹⁴⁶ L. I. Barsky and W. L. Bencze, *J. Med. Chem.* **14**, 40 (1971).

acid as the catalyst. However, Hjelte and Agback¹⁴⁷ obtained the tetrazole **129** as the major product from 1-tetralone, sodium azide, and hydrochloric acid (see Section II,D, 2).

The reaction of naphthoquinones with sodium azide and acetic acid was reported¹⁴⁸ to give only aminonaphthoquinones. Folkers and co-workers¹⁴⁹ were able to carry out the normal Schmidt rearrangement with 1,4-naphthoquinones using concentrated sulfuric acid; **130** ($R^1 = H$; $R^2 = Me$) gave a lactam claimed to be **131** ($R^1 = H$; $R^2 = Me$). However,

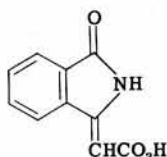


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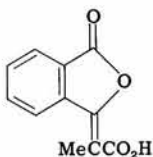


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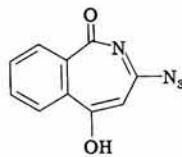
it was shown independently by Rickards and Smith¹⁵⁰ and by Bedford *et al.*¹⁵¹ that the correct structure for the product is **10** ($R^1 = R^2 = R^4 = R^5 = H$; $R^3 = Me$). However, small amounts of the corresponding 2-benzazepin-1-ones were also formed. Similar reactions with related compounds have been reported.^{152,153} Hydroxy-substituted **130** ($R^1 = OH$; $R^2 = H$) and **130** ($R^1 = OH$; $R^2 = Me$) did not undergo the ring expansion. Instead, ring contraction occurred to give **132** and **133**, respectively,



(132)



(133)



(134)

when sodium azide was added to the naphthoquinones in sulfuric acid. When the addition was reversed, the azido compound **134** was isolated

¹⁴⁷ N. S. Hjelte and T. Agback, *Acta Chem. Scand.* **18**, 191 (1964).

¹⁴⁸ L. F. Fieser and J. L. Hartwell, *J. Amer. Chem. Soc.* **57**, 1482 (1935).

¹⁴⁹ D. Misiti, H. W. Moore, and K. Folkers, *Tetrahedron Lett.* 1071 (1965); *Tetrahedron* **22**, 1201 (1966).

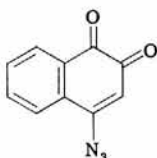
¹⁵⁰ R. W. Rickards and R. M. Smith, *Tetrahedron Lett.*, 2361 (1966).

¹⁵¹ G. R. Bedford, G. Jones, and B. R. Webster, *Tetrahedron Lett.*, 2367 (1966).

¹⁵² G. Jones, *J. Chem. Soc. C*, 1808 (1967).

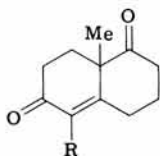
¹⁵³ E. J. Moriconi and I. A. Maniscalco, *J. Org. Chem.* **37**, 208 (1972).

in addition to **132**. The suggested mechanism^{154,155} for these conversions is discussed in Section III,A. 2. 4-Azido-1,2-naphthoquinone (**135**) treated with concentrated sulfuric acid gave¹⁵⁵ an 82% yield of **10** ($R^1 = R^2 =$

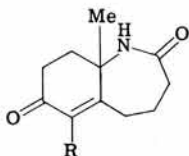


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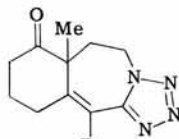
$R^4 = R^5 = H$; $R^3 = OH$). A study of the Schmidt rearrangement of the diketone **136** ($R = H, Me$) showed that by choosing catalysts of different acidities either of the carbonyl groups can be made to react with hydrazoic acid to give all three isomeric benzazepines.¹⁵⁶ Thus, sulfuric acid and sodium azide converted **136** ($R = H, Me$) into **137** ($R = H, Me$), while the use of hydrochloric acid afforded only the tetrazole **138** ($R = H$,



(136)



(137)



(138)

Me). These results are in agreement with the previous observations concerning the effect of the catalyst on the reaction course.^{104,132,137,144a,b,c,147}

2. 2-Benzazepines

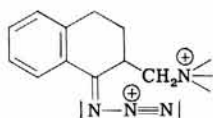
In contrast to the action of sulfuric acid in the reaction of **125** ($R^1-R^5 = H$) with sodium azide, which was reported^{104,131,132} to give 1-benzazepin-2-one (**5**, $R^1-R^8 = H$), the reaction with hydrochloric acid as catalyst-solvent afforded the tetrazole **129**. The treatment of the latter with lithium aluminum hydride¹⁴⁷ gave **19** ($R^1-R^7 = H$). An interesting example of the exclusive formation of 2-benzazepines has been reported by Schmid *et al.* The tetralone **125** ($R^1 =$ piperidinomethyl, 2-piperidinoethyl;

¹⁵⁴ H. W. Moore and H. R. Shelden, *J. Org. Chem.* **32**, 3603 (1967); *Tetrahedron Lett.*, 5431 (1968).

¹⁵⁵ H. W. Moore, H. R. Shelden, and W. Weyler, *Tetrahedron Lett.*, 1243 (1969).

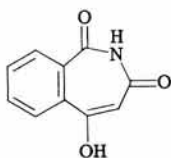
¹⁵⁶ C. V. Greco and R. P. Gray, *Tetrahedron* **26**, 4329 (1970).

$R^2-R^5 = H$) was rearranged by sulfuric acid into **18** ($R^1 =$ piperidino-methyl, 2-piperidinoethyl; $R^2 = H$); trichloroacetic acid was not satisfactory. It was suggested that preferential alkyl migration occurs owing to electrostatic repulsion of the positively charged nitrogens in the intermediate **139** forcing the azido group to assume the *syn*-aryl configuration and

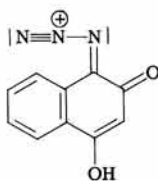


(139)

thus promoting the alkyl migration.¹⁵⁷ A study by Uyco and co-workers,^{144a} discussed in section II,D, 1, suggests that strongly electron-releasing substituents in the aromatic ring of 1-tetralones favor alkyl migration and thus the formation of 2-benzazepin-1-ones. However, considering the report of Evans and Lockhart¹²⁵ that a nitrogen-containing substituent can reverse the effect of an ether in the aromatic ring of 1-tetralone to lead to exclusively 1-benzazepin-2-ones, and those of Schmid *et al.*¹⁵⁷ and Uyco and co-workers^{144a} discussed above, a rather confusing picture emerges as to the course of the Schmidt rearrangement of substituted 1-tetralones. Numerous examples of the formation of both 1- and 2-benzazepinones by the Schmidt reaction have been reported.^{117, 143-146} The reported results¹⁴⁹ on the rearrangement of naphthoquinones into 2-benzazepine-1,5-diones have been shown^{150, 151} to be erroneous, the lactams being 1-benzazepine-2,5-diones. The reaction of **130** ($R^1 = OH$; $R^2 = H$) with hydrazoic acid in sulfuric acid^{154, 155} gave **140** in addition to **132** involving the intermediate cation **141** (see Section III,A, 2). The



(140)



(141)

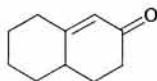
rearrangement of the bicyclic unsaturated ketones **142-145**,¹⁵⁸ **146**,¹⁵⁹

¹⁵⁷ H. J. Schmid, A. Hunger, and K. Hoffmann, *Helv. Chim. Acta* **39**, 607 (1956).

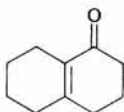
¹⁵⁸ K. Mitsuhashi, K. Nomura, N. Minami, and M. Matsuyama, *Chem. Pharm. Bull.* **17**, 1578 (1969).

¹⁵⁹ K. Mitsuhashi, K. Nomura, and F. Miyoshi, *Chem. Pharm. Bull.* **19**, 1983 (1971).

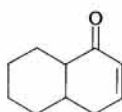
and **147**¹⁶⁰ has been studied. Mixtures of 2- and 3-benzazepinones were



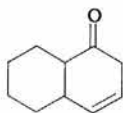
(142)



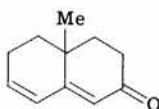
(143)



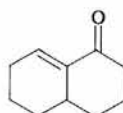
(144)



(145)



(146)

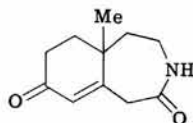


(147)

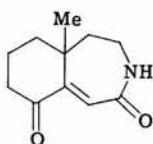
obtained in low yields and a theory was advanced to explain the reaction course depending on the position of the double bonds in the respective ketone.¹⁵⁸

3. 3-Benzazepines

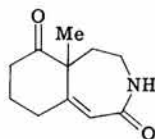
Formation of 3-benzazepines in the Schmidt rearrangement occurs in low yield, and gives a mixture of isomeric benzazepines. The diones **148** and **149** were obtained¹⁵⁹ from **146**, and **150** was prepared¹⁵⁶ from **136**



(148)



(149)



(150)

(R = H).

E. RING ENLARGEMENT

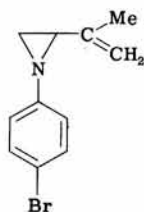
The expansion of smaller rings into the heterocyclic ring of the benzazepines has been achieved with aziridine, indole, quinoline, and isoquinoline systems, usually in high yields, and benzazepines with the highest degree

¹⁶⁰ K. Mitsuhashi, K. Nomura, I. Watanabe, and N. Minami, *Chem. Pharm. Bull.* **17**, 1572 (1969).

of unsaturation can thus be prepared. Only direct enlargements are discussed in this section. The studies, e.g., by von Braun,⁴ in which the benzazepines were prepared from material obtained by ring cleavage of lower-membered systems followed by further chemical manipulations to extend the carbon chain, are discussed in sections II,A.

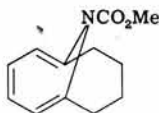
1. 1-Benzazepines

Scheiner¹⁶¹ reported that the infrequently observed amino Claisen rearrangement took place when **151** was refluxed in xylene, to give a 95% yield of **61** ($R^1 = R^2 = R^3 = R^5 = H$; $R^4 = Me$; $R^6 = Br$). The

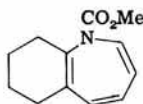


(151)

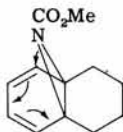
pyrolysis of the bridged azepine **152** in a sealed tube at 180° afforded **153** in 87% yield via **154** and **155**.¹⁶²



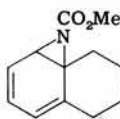
(152)



(153)



(154)



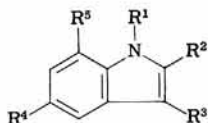
(155)

Although the Diels–Alder reaction of indoles had been investigated

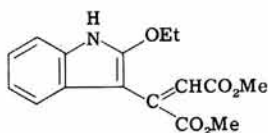
¹⁶¹ P. Scheiner, *J. Org. Chem.* **32**, 2628 (1967).

¹⁶² L. A. Paquette, D. E. Kuhla, and J. H. Barrett, *J. Org. Chem.* **34**, 2879 (1969).

before, Plieninger and Wild¹⁶³ were the first to report that a ring expansion took place during this reaction. Thus, **156** ($R^1 = R^3 = R^4 = R^5 = H$; $R^2 = OEt$) refluxed with dimethyl acetylenedicarboxylate in dioxane gave **65** ($R^1 = OEt$, $R^2 = R^3 = CO_2Me$) in addition to geometric isomers of **157**. When the reaction was carried out with *N*-substituted indole **156**

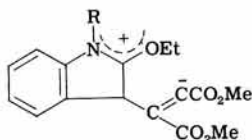


(156)

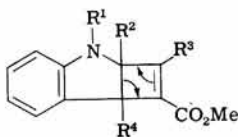


(157)

($R^1 = Me$; $R^2 = OEt$; $R^3 = R^4 = R^5 = H$) the only reaction product, obtained in 72% yield, was **1** ($R^1 = Me$; $R^2 = OEt$; $R^3 = R^4 = CO_2Me$; $R^5 = H$). It is suggested that the acetylene dicarboxylate attacks the indole at the 3-position to form the dipolar adduct **158** ($R = H$, Me),



(158)



(159)

which undergoes ring closure to give **159** ($R^1 = H$, Me ; $R^2 = OEt$; $R^3 = CO_2Me$; $R^4 = H$). The latter collapses as indicated into the 1-benzazepine. It has, however, been reported that a similar reaction with oxindole did not proceed satisfactorily.¹⁶⁴ Lin and Snieckus¹⁶⁵ reacted **156** ($R^1 = Ac$; $R^2 = R^4 = R^5 = H$; $R^3 = \text{piperidino}$) in a similar manner with methyl propiolate to obtain a 68% yield of **1** ($R^1 = Ac$; $R^2 = R^3 = H$; $R^4 = CO_2Me$; $R^5 = \text{piperidino}$). In fact, these authors were able to isolate a derivative of the proposed¹⁶³ cyclobutenoindoles intermediate, i.e., **159** ($R^1 = Ac$; $R^2 = R^3 = H$; $R^4 = \text{piperidino}$) and to confirm the structure by NMR.

Acheson *et al.*¹⁶⁶ studied the Diels-Alder reaction of 2-unsubstituted

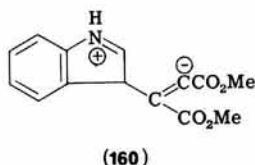
¹⁶³ H. Plieninger and D. Wild, *Chem. Ber.* **99**, 3070 (1966).

¹⁶⁴ E. Winterfeldt and J. M. Nelke, *Chem. Ber.* **103**, 1183 (1970).

¹⁶⁵ M.-S. Lin and V. Snieckus, *J. Org. Chem.* **36**, 645 (1971).

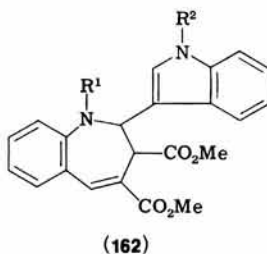
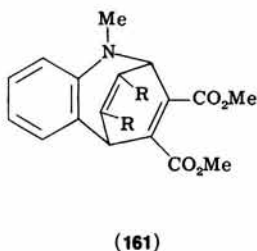
¹⁶⁶ R. M. Acheson, J. N. Bridson, and T. S. Cameron, *J. Chem. Soc. C*, 968 (1972); *J. Chem. Soc. D*, 1225 (1971); R. M. Acheson, *Advan. Heterocycl. Chem.* **1**, 138 (1963); R. M. Acheson, J. N. Bridson, T. R. Cecil, and A. R. Hands, *J. Chem. Soc., Perkin Trans. I*, 1569 (1972).

indoles in detail. While confirming the suggested¹⁶³ pathway of the reaction via the cyclobutenoidole intermediate, these authors propose an indolenine zwitterion **160** from which the corresponding cyclobutenoidole arises



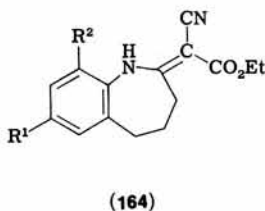
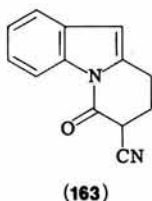
via a nonconcerted process.

The reaction of **156** ($R^1 = \text{Me}$; $R^2\text{--}R^5 = \text{H}$) with dimethyl acetylenedicarboxylate in the absence of solvent or in dry acetonitrile yielded **1** ($R^1 = \text{Me}$; $R^2 = R^5 = \text{H}$; $R^3 = R^4 = \text{CO}_2\text{Me}$) and small quantities of **161** ($R = \text{CO}_2\text{Me}$). The adduct **162** ($R^1 = R^2 = \text{Me}$) was the major



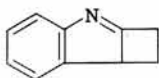
product of the reaction carried out in undried acetonitrile. Indole (**156**) ($R^1\text{--}R^5 = \text{H}$) gave **162** ($R^1 = R^2 = \text{H}$) as the only product both in the dry or undried solvent.¹⁶⁶ Boron trifluoride etherate was used to catalyze the Diels-Alder reaction of 1,2,3-trimethyl-, and 1,3-dimethylindole, respectively, with dimethyl acetylenedicarboxylate.¹⁶⁷

Sakan *et al.*¹⁶⁸ reported an unusual and novel ring closure-expansion of tosylated 2-hydroxyethylindoles. While **156** ($R^1 = R^3 = R^4 = R^5 = \text{H}$; $R^2 = \text{CH}_2\text{CH}_2\text{OTs}$) with ethyl cyanoacetate in the presence of sodium ethoxide in ethanol gave **163**, aromatic-substituted **156** ($R^1 = R^3 = \text{H}$; $R^2 = \text{CH}_2\text{CH}_2\text{OTs}$; $R^4, R^5 = \text{H, OMe}$) afforded **164** ($R^1, R^2 = \text{H, OMe}$)



¹⁶⁷ F. Fried, J. B. Taylor, and R. Westwood, *J. Chem. Soc. D*, 1226 (1971).

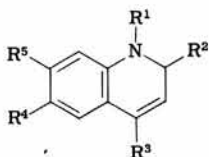
under the same reaction conditions, and 2-tosyloxyethylindole **156**, $R^1 = R^3 = R^4 = R^5 = H$; $R^2 = CH_2CH_2OTs$) in dimethyl sulfoxide gave **164** ($R^1 = R^2 = H$). It was proposed that the cyclobutanoindolenine **165**, arising from the intramolecular electrophilic reaction of the tosylate, is



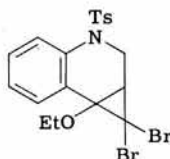
(165)

attacked by the cyanoacetate carbanion followed by expansion of the five-membered ring.¹⁶⁸

Proctor and co-workers¹⁶⁹ developed a method for expanding the quinoline ring. The treatment of **166** ($R^1 = Ts$; $R^2 = R^4 = R^5 = H$;

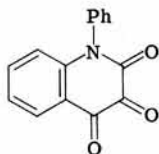


(166)

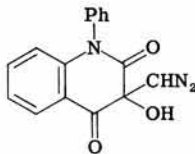


(167)

$R^3 = OEt$) with tribromomethylphenylmercury in refluxing benzene gave **167**, which with silver nitrate in refluxing aqueous ethanol yielded **54** ($R^1 = Ts$; $R^2 = Br$), while refluxing pyridine gave **1** ($R^1 = Ts$; $R^2 = R^3 = H$; $R^4 = Br$; $R^5 = OEt$). Aromatic-substituted 1-benzazepines were prepared similarly. The reaction proceeded also with 2-substituted quinolines; however, for steric reasons, the tosyl group had to be replaced by mesyl to prepare **1** ($R^1 = Ms$; $R^2 = Me$; $R^3 = H$; $R^4 = Br$; $R^5 = OEt$). Eistert and Donath¹⁷⁰ reacted **168** with diazomethane to obtain **169**, which gave



(168)



(169)

¹⁶⁸ T. Sakan, S. Matsubara, H. Takagi, Y. Tokunaga, and T. Miwa, *Tetrahedron Lett.*, 4925 (1968).

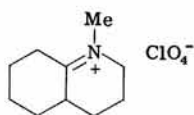
¹⁶⁹ A. Cromarty and G. R. Proctor, *Chem. Commun.*, 842 (1968); A. Cromarty, K. E. Haque, and G. R. Proctor, *J. Chem. Soc. C*, 3536 (1971).

¹⁷⁰ B. Eistert and P. Donath, *Chem. Ber.* **103**, 993 (1970).

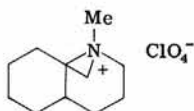
10 ($R^1 = \text{Ph}$; $R^2 = R^4 = R^5 = \text{H}$; $R^3 = \text{OH}$) in 84% yield on treatment with methanol or ethanol at room temperature.

2. 2-Benzazepines

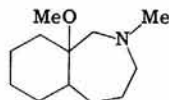
The perchlorate **170** was treated with diazomethane in methylene chloride to give **171** which, refluxed in methanol followed by treatment with sodium hydroxide, gave a 68% yield of **172**.¹⁷¹



(170)



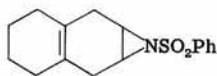
(171)



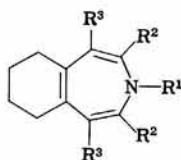
(172)

3. 3-Benzazepines

Paquette *et al.*¹⁷² reacted the aziridine **173** with bromine in methylene chloride followed by dehydrobromination with potassium *t*-butoxide to obtain **174** ($R^1 = \text{SO}_2\text{Ph}$; $R^2 = R^3 = \text{H}$).

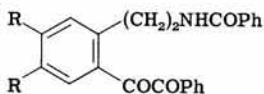


(173)

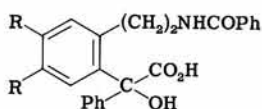


(174)

An elaborate but effective method of expanding the isoquinoline ring has been reported by Chazerain.²⁸ The dihydroisoquinoline **100** ($R^1 = R^2 = \text{OEt}$) was converted by benzoyl chloride into the benzil **175** ($R = \text{OEt}$) which by a benzilic rearrangement gave **176** ($R = \text{OEt}$); debenzoyla-



(175)

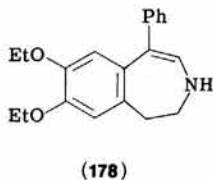
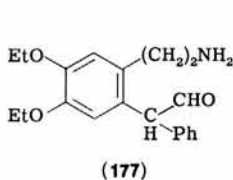


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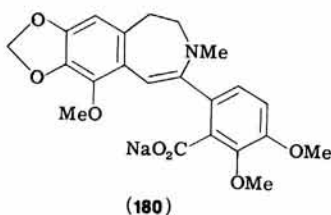
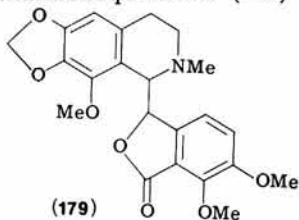
¹⁷¹ N. J. Leonard, K. Jann, J. V. Paukstelis, and C. K. Steinhardt, *J. Org. Chem.* **28**, 1499 (1963).

¹⁷² L. A. Paquette, D. E. Kuhla, J. H. Barrett, and R. J. Haluska, *J. Org. Chem.* **34**, 2866 (1969).

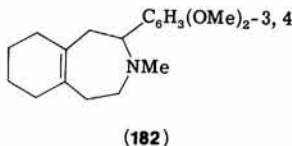
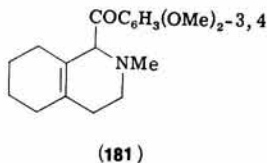
tion and thermal cyclization of the latter gave **34** ($R^1 = \text{Ph}$; $R^2 = \text{OH}$, $R^3\text{--}R^7 = \text{H}$; $R^8 = R^9 = \text{OEt}$; $R^{10} = \text{H}$) in addition to 1-carboxy-1-phenyl- and 1-phenyl-1,2,3,4-tetrahydroisoquinoline, respectively. The formation of the isoquinolines could be avoided by removing the tertiary hydroxyl group in **176** ($R = \text{OEt}$) followed by the lactamization of the reduced product. Alternatively, **177** was prepared by the usual reactions from **176** ($R = \text{OEt}$) and thermally cyclized to give **178**. The synthesis



was modified by Hamon^{29,30} who reduced the benzil **175** ($R = \text{OEt}$) to obtain the corresponding diol, which underwent the pinacol rearrangement and ring closure, using 85% phosphoric acid, to give **178**. However, isoquinoline derivatives were also formed and it was concluded that the reaction was dependent on the nature of the aromatic substituent and on the strength of the acid used in the reaction. Analogous ring expansion of the isoquinoline system has been reported recently¹⁷³ to convert the phthalisoquinoline (**179**) into **180** and to synthesize rhoeadine-type



alkaloids.¹⁷⁴ Grewe and Winter¹⁷⁵ observed a ring enlargement during the reduction of **181** with zinc and acetic acid to obtain **182** in 80% yield.

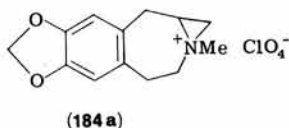
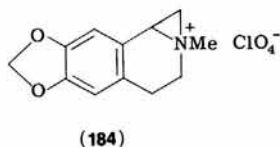
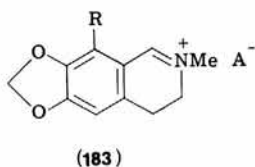


¹⁷³ W. Kloetzer, S. Teitel, J. F. Blount, and A. Brossi, *Monatsh. Chem.* **103**, 435 (1972); *J. Amer. Chem. Soc.* **93**, 4321 (1971).

¹⁷⁴ H. Irie, S. Tani, and H. Yamane, *J. Chem. Soc. D*, 1713 (1970).

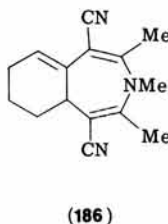
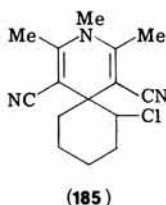
¹⁷⁵ R. Grewe and G. Winter, *Chem. Ber.* **92**, 1092 (1959).

Similar reduction–ring expansion was carried out with variously substituted isoquinolines, the acetic acid being replaced by propionic acid.¹⁷⁶ Goeber *et al.*¹⁷⁷ expanded the ring of the isoquinolinium salt **183** ($R = H$, OMe ; $A = OH$) on treatment with phenyldiazomethane in methanol to prepare **35** ($R^1 = R^2 = H$; $R^3 = Me$; $R^4 = Ph$; $R^5 = OMe$; $R^6 = H$, Me ; R^7 , $R^8 = O-CH_2-O$). Similarly, **183** ($R = H$, $A = ClO_4$) treated with diazomethane gave a mixture of **184** and **184a**. The crude mixture of these



products with methanol or water gave **35** ($R^1 = R^2 = R^4 = R^6 = H$; $R^3 = Me$; $R^5 = OMe$, OH ; R^7 , $R^8 = O-CH_2-O$) and with lithium aluminum hydride gave **35** ($R^1 = R^2 = R^5 = R^6 = H$; $R^3 = R^4 = Me$; R^7 , $R^8 = O-CH_2-O$). The reaction, however, did not proceed with phenyldiazomethane.¹⁷⁸

Treatment of the spiropyridine (**185**) with potassium *t*-butoxide in 1,2-dimethoxyethane afforded a 51% yield of **186** which with trifluoro-



¹⁷⁶ C. Reby and M. J. Gardent, *Bull. Soc. Chim. Fr.*, 1574 (1972).

¹⁷⁷ B. Goeber, S. Pfeifer, V. Hanuš, and G. Engelhardt, *Arch. Pharm. (Weinheim)* **301**, 763 (1968); B. Goeber and G. Engelhardt, *Pharmazie* **24**, 423 (1969).

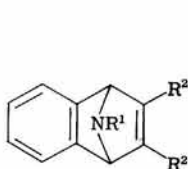
¹⁷⁸ H. O. Bernhard and V. Snieckus, *Tetrahedron* **27**, 2091 (1971).

acetic acid in chloroform yielded the isomer **174** ($R^1 = R^2 = \text{Me}$; $R^3 = \text{CN}$).¹⁷⁹

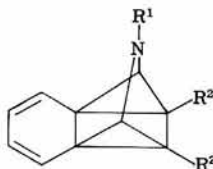
F. REARRANGEMENT

3-Benzazepines

The direct photoexcitation of **187** ($R^1 = \text{CO}_2\text{Me}$, Ts; $R^2 = \text{H}$, CO_2Me) resulted in a rearranged product, i.e., **3** ($R^1 = R^5 = \text{H}$, CO_2Me ; $R^2 = R^4 = \text{H}$; $R^3 = \text{CO}_2\text{Me}$, Ts), formed in low yield via **188** ($R^1 = \text{CO}_2\text{Me}$,



(187)



(188)

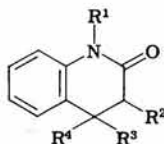
Ts; $R^2 = \text{H}$, CO_2Me).¹⁸⁰ Silver nitrate in methanol converts the anti isomer of **187** ($R^1 = \text{Cl}$; $R^2 = \text{H}$) into a product tentatively identified as 1-methoxy-1-benzazepine (**1**, $R^1 = \text{OMe}$; $R^2 = R^3 = R^4 = R^5 = \text{H}$).^{180a}

III. Reactions

A. RING CONTRACTION

1. 1-Benzazepines

Horning⁹ described the ring contraction of **5** ($R^1\text{--}R^3 = \text{H}$; $R^4 = \text{CO}_2\text{Me}$; $R^5\text{--}R^8 = \text{H}$) into the indole **14** by the action of hot hydrochloric acid. On the other hand, the 4-substituted 1-benzazepin-2-one **5** ($R^1 = R^2 = \text{H}$; $R^3 = \text{CO}_2\text{H}$; $R^4\text{--}R^8 = \text{H}$) afforded the quinolone **189** ($R^1 = R^3 = R^4 = \text{H}$;



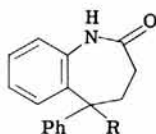
(189)

¹⁷⁹ A. W. Johnson and M. Mahendran, *J. Chem. Soc. C*, 1237 (1971); *J. Chem. Soc. D*, 10 (1970).

¹⁸⁰ G. Kaupp, J. Perreten, R. Leute, and H. Prinzbach, *Chem. Ber.* **103**, 2288 (1970).

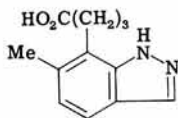
^{180a} V. Rautenstrauch, *Chem. Commun.*, 1122 (1969).

$R^2 = \text{CO}_2\text{H}$) under the same reaction conditions.¹⁰⁸ It has been suggested that the ring contraction is due to a direct, acid-catalyzed intramolecular ester-amide exchange rather than hydrolytic ring-opening and subsequent recyclization.^{9,108} Analogous ring contractions have been observed¹⁰⁹: **190** ($R = \text{CO}_2\text{Et}$) treated with acid gave 3-phenyl-substituted **14** while

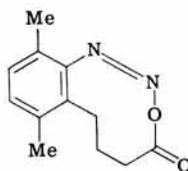


(190)

190 ($R = \text{CH}_2\text{CO}_2\text{Et}$), under the same conditions, afforded **189** ($R^1 = R^2 = \text{H}$; $R^3 = \text{Ph}$; $R^4 = \text{CH}_2\text{CH}_2\text{CO}_2\text{H}$). Gordon *et al.*¹⁸¹ obtained the indazole **191** when **5** ($R^1\text{--}R^4 = \text{H}$; $R^5 = R^8 = \text{Me}$; $R^6 = R^7 = \text{H}$) was nitrosated with sulfuric acid-nitric acid-sodium azide mixture and the *N*-nitroso derivative was allowed to stand in benzene for 7 days. The intermediate **192**, previously described by Huisgen,¹⁸² was implicated in



(191)



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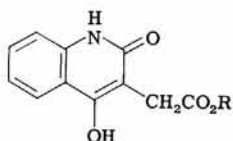
the ring contraction.¹⁸¹ Look¹⁸³ obtained methyl quinaldate on an attempted hydrolysis of 2,3,3-trimethoxy-3*H*-1-benzazepine to the benzazepin-3-one. Other reports have appeared describing the ring contraction of derivatives of 1-benzazepin-5-one,¹¹² 1-benzazepin-2-one,⁴⁵ 1-benzazepine-2,3-dione,¹⁸⁴ and 1-benzazepine-2,5-dione,¹⁵⁵ respectively, into the appropriate quinoline derivatives. Geissman and Cho⁴⁷ attempted the hydrolysis of **9** ($R^1 = \text{CO}_2\text{Me}$, CO_2Et ; $R^2 = R^3 = \text{H}$) in acid or base and obtained **193** ($R = \text{H}$), while **56** ($R^1 = R^4 = \text{H}$; $R^2 = \text{CO}_2\text{Me}$; $R^3 = \text{OMe}$) on acidic hydrolysis yielded **193** ($R = \text{Me}$) but alkaline hydrolysis gave **56** ($R^1 = R^4 = \text{H}$; $R^2 = \text{CO}_2\text{H}$; $R^3 = \text{OMe}$). Vogel *et al.*¹¹⁷ suggested a mechanism of the

¹⁸¹ D. Gordon, L. Frye, and H. Sheffer, *Acta Chem. Scand.* **23**, 3577 (1969).

¹⁸² R. Huisgen, *Ann. Chem.* **574**, 171 (1951).

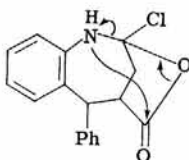
¹⁸³ M. Look, *Diss. Abstr.* **17**, 35 (1957).

¹⁸⁴ C. G. Hughes and A. H. Rees, *Chem. Ind. (London)* 1439 (1971).



(193)

observed ring contraction of **5** ($R^1 = R^2 = H$; $R^3 = CO_2H$; $R^4 = Ph$; $R^5-R^8 = H$). Heating of the latter with thionyl chloride and pyridine in dimethyl formamide, followed by treatment with dimethylamine, gave **189** ($R^1 = R^4 = H$; $R^2 = CH_2CONMe_2$; $R^3 = Ph$). However, only **5** ($R^1 = R^2 = H$; $R^3 = CONMe_2$; $R^4 = Ph$; $R^5-R^8 = H$) was obtained when all the above reaction components were present in the mixture and mild reaction conditions ($\sim 20^\circ$) were employed. It has been suggested that the lactone **194** is the intermediate which undergoes ring contraction as



(194)

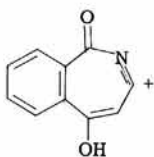
indicated.¹¹⁷ Uyeo *et al.*¹⁸⁵ described the ring contraction of **7** ($R^1 = R^2 = H$) upon dehydrogenation with 40% palladium on charcoal in ethyl cinnamate, into a mixture of quinoline derivatives. *N*-Tosyl-1,2-dihydro-3*H*-1-benzazepin-3-one treated with sodium methoxide afforded quinoline-2-carboxaldehyde.¹⁸⁶

2. 2-Benzazepines

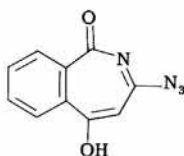
Moore and Shelden¹⁵⁴ described a ring contraction during the attempted preparation of hydroxy-substituted benzazepinediones by the Schmidt rearrangement of **130** ($R^1 = OH$; $R^2 = H$) and **130** ($R^1 = OH$; $R^2 = Me$), respectively; they obtained only ring-contracted products **132** and **133**. It was suggested that the ring contraction may proceed via the cation **195**, which reacts with another mole of hydrazoic acid to give the azide **196**. The latter on hydrolysis affords **197**, which is cleaved in acidic reaction medium to give **198** ($R = H$) followed by recyclization into **132**. Because of the more sterically hindered ketone group in **198** ($R = Me$) formed by this reaction pathway from **130** ($R^1 = OH$; $R^2 = Me$), the

¹⁸⁵ S. Uyeo, T. Shingu, and H. Harada, *Yakugaku Zasshi* **85**, 314 (1965); *Chem. Abstr.* **63**, 4250 (1965).

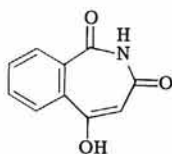
¹⁸⁶ M. A. Rehman, *J. Natur. Sci. Math.* **9**, 297 (1969); *Chem. Abstr.* **73**, 87764f (1970).



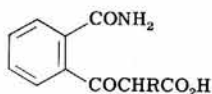
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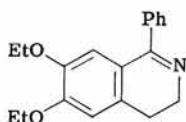


(198)

recyclization product is **133**. However, later it was suggested¹⁵⁵ that the cation **141** is the intermediate in the formation of both **197** and **132**, and that the reactive site of **130** ($R^1 = OH$; $R^2 = H$) is at C-1 and not C-2 as previously suggested.¹⁵⁴

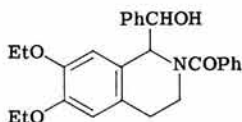
3. 3-Benzazepines

Oxidation of an ethereal solution of **178** in air in the presence of acid gives the isoquinoline **199**. Aromatic-unsubstituted 3-benzazepines are



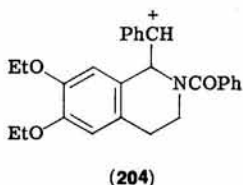
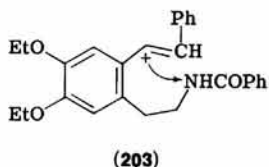
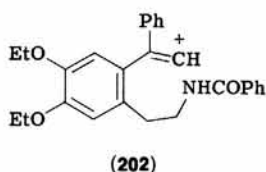
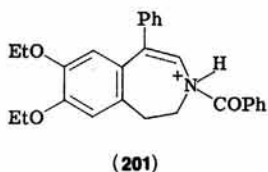
(199)

even more sensitive to the oxidation.^{28,29} The prolonged action of 85% phosphoric acid converts *N*-benzoyl derivatives of **178** by Wagner-Meerwein type rearrangement^{29,30} into **200**. A reaction mechanism has

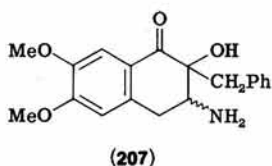
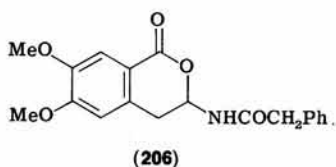
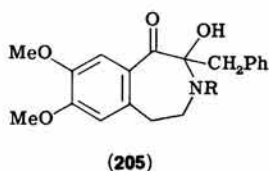


(200)

been suggested as follows: The nitrogen of **178** is attacked by acid to give the cation **201** followed by ring cleavage to $202 \rightleftharpoons 203$ and recyclization into the cation **204**, which undergoes solvation.^{29,30} Oxidation of **205**



(R = H) with periodic acid gave⁹⁴ **206**. Attempted demesylation of **205**

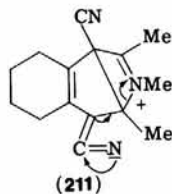
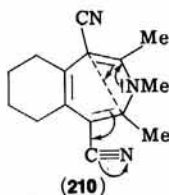
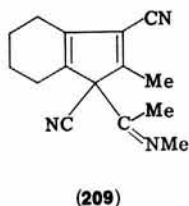


(R = SO₂Me) with potassium hydroxide resulted in ring contraction to yield¹⁸⁷ **207**. The hydrolysis of **99** under a variety of conditions afforded⁹⁵ **100** (R¹ = R² = OMe). The action of strong mineral acids on **3** (R¹ = R⁵ = H; R² = R⁴ = CO₂H; R³ = Me) gave **208**, while the *N*-phenyl



¹⁸⁷ J. Gardent, G. Hazebrucq, and G. Cormier, *Bull. Soc. Chim. Fr.*, 4001 (1969).

derivative **3** ($R^1 = R^5 = H$; $R^2 = R^4 = CO_2H$; $R^3 = Ph$) remained unchanged.^{96b} Refluxing **174** ($R^1 = R^2 = Me$; $R^3 = CN$) in xylene for 5 days afforded **209** by a suggested mechanism¹⁷⁹ shown in **210** or **211**.



B. RING-OPENING

The hydrolytic opening of the heterocyclic ring of the isomeric benzazepines can be achieved under alkaline or acidic conditions at temperatures varying from ambient to high. A striking difference has been reported in the hydrolysis of 1-benzazepin-2-ones as compared to 2-benzazepin-1-ones. The former are 90% hydrolyzed in 2 *N* hydrochloric acid at room temperature in 48 hours while the latter remain essentially unchanged after 3 weeks.^{125,145} Examples have been described of the differences in the feasibility of ring-opening of saturated benzazepines having no amido bond in the molecule and those having the lactam structure.^{4-7,131} It has been reported that the reduction of the carbonyl group in **5** ($R^1-R^8 = H$) with sodium in alcohol results in the formation of 4-(2-aminophenyl)butyl alcohol.⁶ The action of ozone and alkaline hydrogen peroxide resulting in ring-opening of 1-benzazepines has been reported.¹⁸⁸ The presence of a double bond in the heterocyclic ring renders it stable to hydrolysis.²⁵ 3-Benzazepines of the highest degree of unsaturation are stable in cold or hot acids,^{96a} while those partially saturated can be hydrolyzed.^{20,21}

IV. Physical Properties

Coefficients of linear combination, charge density, bond order, free valency, N-H valency vibration, and atom localization energy were calculated for **1** ($R^1-R^5 = H$) by the use of the simple Hückel LCAO-MO pattern. The data suggest that there is a strong localization of π -electrons of nitrogen and of double bonds in the seven-membered ring.¹⁸⁹ Dewar and Trinajstić carried out calculations of ground states of **1** ($R^1-R^5 = H$), **2**, and **3** ($R^1-R^5 = H$) by a semiempirical SCF-MO method. The results

¹⁸⁸ G. R. Proctor, *J. Chem. Soc.*, 3989 (1961).

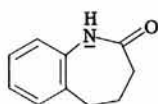
¹⁸⁹ R. W. Schmid, *Helv. Chim. Acta* **45**, 1982 (1962).

imply that these ring systems are not aromatic as would be expected since they are isoconjugate with the benzotropylium anion.¹⁹⁰

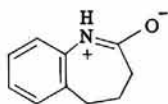
The conformation of the seven-membered ring of **7** ($R^1, R^2 = H, Me$) has been suggested to be in the chair form.⁵⁵

The pK_a (5.50) of **1** ($R^1-R^5 = H$) in water at 18.6° was determined and compared with those of other amines on the basis of the different extent of conjugation of nitrogen with the aromatic ring due to steric effects.¹⁹¹

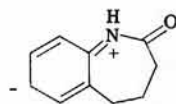
Huisgen *et al.* formulated **5** ($R^1-R^8 = H$) as the resonance hybrid **212** \leftrightarrow **213** \leftrightarrow **214** and discussed UV spectra, reactivity, and basicity of



(212)



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(214)

this benzazepinone on the basis of this mesomerism.¹⁰⁴

X-Ray diffraction study and molecular parameters for **162** ($R^1 = R^2 = H$) have been described.¹⁶⁶

It has been claimed that IR spectra are useful in distinguishing 1-benzazepin-2-ones from 2-benzazepin-1-ones. The former show CO absorption at higher frequency (15 to ~ 20 cm^{-1}) than the latter.^{116, 143} IR spectra of derivatives of 1-benzazepine,^{7, 43a, 43b, 46, 53, 103, 108, 150} 2-benzazepine,^{70, 103, 116, 143} and 3-benzazepine^{20, 22} have been recorded and discussed.

The UV spectrum of 1-benzazepin-2-one (**5**) ($R^1-R^8 = H$) was studied in detail by Huisgen *et al.*¹⁰⁴ A shift in the absorption by ~ 10 $m\mu$ towards shorter wavelength was observed as compared to acetanilide. Other authors reported UV data for derivatives of 1-benzazepine,^{7, 43a, 43b, 49, 103, 104, 150} 2-benzazepine,^{103, 104} and 3-benzazepine.^{20, 96a}

NMR spectra have been recorded for derivatives of 1-benzazepine,^{55, 116, 117, 143, 150, 163, 165, 169} 2-benzazepine,^{13, 25, 62a, 116} and 3-benzazepine.^{20, 22, 27, 76, 95, 176}

Deuterium exchange of the N-H proton proved to be of value to distinguish between 1-benzazepin-2-one and 2-benzazepin-1-one derivatives. The multiplet at 2.3–2.1 ppm assigned to $NHCOCH_2CH_2$ in the former did not change in contrast to the latter, where a significant change was observed in the 3.4–3.0 ppm region assigned to $CONHCH_2CH_2$.¹⁴³ The resonance of the olefinic protons and cross-carbonyl coupling of derivatives of **10** have been discussed.^{149–151} Temperature-variable NMR spectra of **1** ($R^1 = Ac$; $R^2 = R^3 = H$; $R^4 = CO_2Me$; $R^5 = piperidino$) have been recorded.¹⁶⁵

¹⁹⁰ M. J. S. Dewar and N. Trinajstić, *Tetrahedron* **26**, 4269 (1970).

¹⁹¹ R. Reynaud and P. Rumpf, *Bull. Soc. Chim. Fr.*, 1805 (1963).

The inversion barrier of 17 kcal/mole has been determined for **1** ($R^1 = \text{Ts}$; $R^2 = R^3 = \text{H}$; $R^4 = \text{Br}$; $R^5 = \text{OEt}$).¹⁶⁹

V. Biological Activity

Derivatives of 1-benzazepine were found to have analgesic,^{192,193} anti-depressant,¹⁹⁴ antifibrillant,^{195,196} antihypertensive,^{197,198} antineoplastic,¹⁹⁹ diuretic,²⁰⁰ hypoglycemic,²⁰¹ and antiarrhythmic^{202,203} activity. Derivatives of 2-benzazepine were assayed on their antihypertensive,^{204,205} adrenergic-blocking,¹⁷ and cholinesterase inhibiting²⁰⁶ activity. Various 3-benzazepine derivatives were prepared as potentially active antihypertensives,^{207,208} hypoglycemics,²⁰⁹⁻²¹⁴ analgesics,^{210,215} depressants,²¹⁶ anoretics^{217,218} and ganglion blocking agents.²¹⁹

¹⁹² U. S. Patent 3,475,414; *Chem. Abstr.* **72**, 3401 (1970).

¹⁹³ U. S. Patent 2,520,264; *Chem. Abstr.* **45**, 675 (1951).

¹⁹⁴ J. Krapcho and C. F. Turk, *J. Med. Chem.* **9**, 191 (1966).

¹⁹⁵ French Patent M3273; *Chem. Abstr.* **65**, 2272 (1966).

¹⁹⁶ U. S. Patent 3,332,951; *Chem. Abstr.* **67**, 100138 (1967).

¹⁹⁷ U. S. Patent 3,093,632; *Chem. Abstr.* **59**, 12771 (1963).

¹⁹⁸ Netherlands Appl. 6,516,320; *Chem. Abstr.* **65**, 15354 (1966).

¹⁹⁹ D. M. James and A. H. Rees, *J. Med. Pharm. Chem.* **5**, 1234 (1962).

²⁰⁰ U. S. Patent 3,458,498; *Chem. Abstr.* **71**, 81225 (1969).

²⁰¹ U. S. Patent 3,509,130; *Chem. Abstr.* **73**, 98832 (1970).

²⁰² W. E. Barrett, T. Garces, and A. J. Plummer, *Arch. Int. Pharmacodyn. Ther.* **182**, 65 (1969).

²⁰³ Ger. Offen. 1,905,525; *Chem. Abstr.* **72**, 12784 (1970).

²⁰⁴ Japanese Patent 7026,739; *Chem. Abstr.* **74**, 53575 (1971).

²⁰⁵ A. Stankevicius, A. Kost, and V. Vizas, *Khim. Farm. Zh.* **3**, 21 (1969); *Chem. Abstr.* **72**, 66776 (1970).

²⁰⁶ Japanese Patent 28,267 (1965); *Chem. Abstr.* **64**, 9696 (1966).

²⁰⁷ U. S. Patent 3,496,166; *Chem. Abstr.* **73**, 14724 (1970).

²⁰⁸ U. S. Patent 3,609,138; *Chem. Abstr.* **75**, 140722 (1971).

²⁰⁹ U. S. Patent 3,575,962; *Chem. Abstr.* **75**, 48938 (1971).

²¹⁰ French Patent 1,535,085; *Chem. Abstr.* **71**, 81224 (1969).

²¹¹ Ger. Offen. 1,921,737; *Chem. Abstr.* **74**, 22817 (1971).

²¹² S. African Patent 67 05,100; *Chem. Abstr.* **70**, 106409 (1969).

²¹³ S. African Patent 67 05,527; *Chem. Abstr.* **70**, 96654 (1969).

²¹⁴ Swiss Patent 485,728; *Chem. Abstr.* **72**, 132570 (1970).

²¹⁵ Ger. Offen. 1,921,861; *Chem. Abstr.* **72**, 31646 (1970).

²¹⁶ T. M. Itil, M. J. Stock, A. D. Duffy, A. Esquenazi, B. Saleuty, and T. H. Han, *Curr. Ther. Res.* **14**, 136 (1972).

²¹⁷ Ger. Offen. 2,016,136; *Chem. Abstr.* **76**, 34136 (1972).

²¹⁸ Swiss Patent 498,123; *Chem. Abstr.* **74**, 125489 (1971).

²¹⁹ British Patent 822,506; *Chem. Abstr.* **54**, 3466 (1960).

Advances in Oxazole Chemistry

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Bundoora, Victoria, Australia*

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I. Introduction

The first review of the chemistry of oxazoles by R. H. Wiley¹ was published in 1945 when the parent molecule was still unknown. A significant interest in the chemistry of oxazoles was revived in an effort to synthesize penicillin, when this fascinating antibiotic molecule was thought to contain an oxazole ring. In this way aspects of oxazole chemistry were studied which had received little or no attention before. An extensive coverage of this work² appeared in 1949. The chemistry of oxazole and its derivatives

¹ R. H. Wiley, *Chem. Rev.* **37**, 401-442 (1945).

² J. W. Cornforth, in "The Chemistry of Penicillin" (H. T. Clarke, J. R. Johnson, and R. Robinson, eds.), Chapter XXI, pp. 688-730. Princeton Univ. Press, Princeton, New Jersey, 1949.

was later reviewed by J. D. Loudon³ in Rodd's "Chemistry of Carbon Compounds," and by J. W. Cornforth⁴ in "Heterocyclic Compounds" edited by Elderfield, the latter being more comprehensive and illustrative in the subject matter coverage. Both of these monographs appeared in 1957 and covered the literature only up to the end of 1955. Several other monographs on the chemistry of heterocyclic compounds⁵⁻⁹ have also dealt with some aspects of oxazole chemistry but in a necessarily brief manner. Specific topics in oxazole chemistry have been covered in further reviews.^{10,11} Advances in the syntheses of alkenyl monomers containing the oxazole nucleus have also been the subject of a short review.¹² Two most recent reviews deal with some of the physicochemical and spectroscopic properties of oxazoles in conjunction with other heterocycles.^{13,14}

The aim of the present review is to survey the numerous developments made in the field of oxazole chemistry from the beginning of 1955 to the end of 1972. The emphasis has been placed on methods of synthesis and reactions of the mononuclear oxazoles; therefore only a few references are given to condensed oxazoles (such as benzoxazoles and naphthoxazoles). No attempt will be made to review the extensive literature on reduced oxazoles, oxazolinones, oxazolidones, and related compounds. This review

³ J. D. Loudon, in "Chemistry of Carbon Compounds" (E. H. Rodd, ed.), Vol. IVA, pp. 353-361. Elsevier, Amsterdam, 1957.

⁴ J. W. Cornforth, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 5, pp. 298-336. Wiley, New York, 1957.

⁵ R. M. Acheson, "Introduction to the Chemistry of Heterocyclic Compounds," 2nd ed. Wiley (Interscience), New York, 1967.

⁶ A. Albert, "Heterocyclic Chemistry, an Introduction," 2nd ed. Athlone Press, London, 1968.

⁷ L. A. Paquette, "Principles of Modern Heterocyclic Chemistry." Benjamin, New York, 1968.

⁸ A. R. Katritzky and J. M. Lagowski, "The Principles of Heterocyclic Chemistry." Methuen, London, 1967.

⁹ M. H. Palmer, "The Structure and Reactions of Heterocyclic Compounds." Edward Arnold, London, 1967.

¹⁰ H. Bredereck, R. Gompper, H. G. von Schuh, and G. Theilig, in "Newer Methods of Preparative Organic Chemistry" (W. Foerst, ed.), Vol. III, p. 241. Academic Press, New York, 1964.

¹¹ M. Ya. Karpeiskii and V. L. Florent'ev, *Usp. Khim.* **38**(7), 1244-1256 (1969); *Russ. Chem. Rev.* **38**(7), 540-546 (1969).

¹² Y. Iwakura, *Senryo To Takuhin* **13**, 391-396 (1968); *Chem. Abstr.* **70**, 46709 (1969).

¹³ A. R. Katritzky, ed., "Physical Methods in Heterocyclic Chemistry," Vol. III. Academic Press, New York, 1971.

¹⁴ A. R. Katritzky, ed., "Physical Methods in Heterocyclic Chemistry," Vol. IV. Academic Press, New York, 1971.

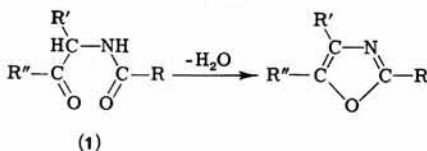
has been planned in such a way as to give the complete chemistry of this heterocycle when combined with the earlier review by Cornforth.⁴

II. Syntheses of the Oxazole Ring System

In the following sections we have attempted to rationalize numerous methods available for the synthesis of oxazoles. It was convenient to classify the syntheses according to the starting materials used rather than adopting the specific bond formations. Occasionally the closely related starting materials have been incorporated under one heading, and scope and limitations have been pointed out.

A. FROM α -ACYLAMINO CARBONYL COMPOUNDS (THE ROBINSON-GABRIEL SYNTHESIS)

One of the classical methods of the formation of oxazoles is the cyclization of α -acylamino carbonyl compounds (1). This synthesis has, in fact, been the subject of oxazole research for more than a century, since the first example of this cyclization is the synthesis of "benzilam" (2,4,5-triphenyloxazole) in 1845 by Laurent.¹⁵ Almost six decades later, Robinson¹⁶ and Gabriel¹⁷ in their independent but systematic investigation of this reaction employed concentrated sulfuric acid and phosphorus pentachloride, respectively, to effect the ring closure.



Apparently, of these two dehydrating agents, sulfuric acid has been adopted more widely¹⁸ because it affords better yields and practically no by-products. Very often this is the reagent of choice for the synthesis

¹⁵ M. Laurent, *J. Prakt. Chem.* **35**, 461 (1845).

¹⁶ R. Robinson, *J. Chem. Soc.* **95**, 2167 (1909).

¹⁷ S. Gabriel, *Ber.* **43**, 134, 1283 (1910).

¹⁸ O. P. Shvaika and G. P. Climisha, *Khim. Geterotsikl. Soedin.* **2**, 677 (1966); *Chem. Heterocycl. Comp.* **2**, 517 (1966).

of 2,5-diaryloxazoles.¹⁹⁻²⁴ Castek and Prostenik²⁵ have prepared some 2,4,5-trialkyloxazoles in 65-90% yields by cyclodehydration of the corresponding α -acylamino ketones with concentrated sulfuric acid. However, the general procedure utilizing sulfuric acid, at or above room temperature, to give the oxazole fails to yield the desired product in certain cases when larger aryl groups are present.²⁶ In such instances the oxazoles were successfully obtained by refluxing the oxo-amides (1) with large excess of phosphorus oxychloride,²⁶ a method which is now used almost exclusively.^{24, 27-34}

The cyclization has also been carried out successfully in the presence of other dehydrating agents³⁵ such as phosphorus pentoxide,³⁶ thionyl chloride,^{37, 38} a mixture of acetic anhydride and concentrated sulfuric

¹⁹ O. Trösken, German Patent 926,249 (1955); *Chem. Abstr.* **52**, 3867 (1958).

²⁰ A.-G. Kalle, British Patent 874,634 (1961); *Chem. Abstr.* **58**, 6833 (1963).

²¹ O. Sues, W. Neugebauer, E. Lind, and K. W. Kluepfel, U.S. Patent 3,257,203 (1966); *Chem. Abstr.* **65**, 16973 (1966).

²² O. Manabe, T. Nagakoshi, and H. Hiyama, *Yuki Gosei Kagaku Kyokai Shi* **26**, 355 (1968); *Chem. Abstr.* **69**, 67291 (1968).

²³ V. G. Chekhuta and A. A. Kuz'menkov, *Metody Poluch. Khim. Reaktivov Prep.* **32**, 98 (1970); *Chem. Abstr.* **77**, 126478 (1972).

²⁴ S. D. Paul and D. L. Dhane, *J. Indian Chem. Soc.* **49**, 279 (1972); *Chem. Abstr.* **77**, 48313 (1972).

²⁵ A. Castek and M. Prostenik, *Bull. Sci., Conseil Acad. RSF Yougoslavie* **11**, 100 (1966); *Chem. Abstr.* **65**, 20115 (1966).

²⁶ F. N. Hayes, B. S. Rogers, and D. G. Ott, *J. Amer. Chem. Soc.* **77**, 1850 (1955).

²⁷ N. Saito and C. Tanaka, *J. Pharm. Soc. Jap.* **76**, 305 (1956); *Chem. Abstr.* **50**, 13873 (1956).

²⁸ C. Tanaka and N. Saito, *Yakugaku Zasshi* **82**, 136 (1962); *Chem. Abstr.* **58**, 3407 (1963).

²⁹ C. Tanaka, *Yakugaku Zasshi* **85**, 186 (1965); *Chem. Abstr.* **62**, 16222 (1965).

³⁰ N. Saito, T. Kurihara, S. Yasuda, K. Yamanaka, S. Tsuruta, T. Tanaka, and Y. Inamori, *Yakugaku Zasshi* **88**, 1610 (1968); *Chem. Abstr.* **70**, 87639 (1969).

³¹ G. Mattalia and E. Marchetti, *Farmaco, Ed. Sci.* **26**, 512 (1971); *Chem. Abstr.* **75**, 76658 (1971).

³² E. Marchetti, German Offen. 2,108,437 (1971); *Chem. Abstr.* **76**, 46188 (1972).

³³ S. E. Kovalev, B. M. Krasovitskii, and E. A. Shevchenko, USSR Patent 327,226 (1972); *Chem. Abstr.* **77**, 36389 (1972).

³⁴ S. D. Paul, D. L. Dhane, K. A. Noras, and A. U. Mushrit, *J. Indian Chem. Soc.* **49**, 579 (1972); *Chem. Abstr.* **77**, 114285 (1972).

³⁵ M. Matsuo, T. Sakaguchi, and T. Akamatsu, German Offen. 2,050,711 (1971); *Chem. Abstr.* **75**, 50423 (1971).

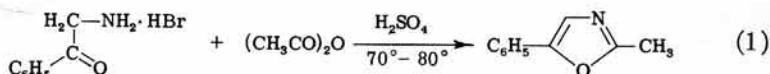
³⁶ F. N. Hayes, L. C. King, and D. E. Peterson, *J. Amer. Chem. Soc.* **74**, 1106 (1952).

³⁷ C. G. Alberti, L. Bernardi, B. Camerino, S. Redaelli, and A. Vercellone, *Gazz. Chim. Ital.* **83**, 922 (1953).

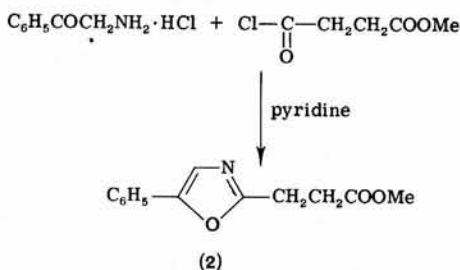
³⁸ F. Korte and K. Störko, *Chem. Ber.* **93**, 1033 (1960).

acid,³⁸⁻⁴⁰ and 98% phosphoric acid in acetic anhydride.⁴¹ The reported yields of oxazoles are from over 60% to almost quantitative.

In one of the modifications⁴⁰ of this method α -aminoacetophenone hydrobromide has been simultaneously acetylated and cyclized in one step by heating with a mixture of acetic anhydride and concentrated sulfuric acid at 70–80°C to give 2-methyl-5-phenyloxazole in good yield [Eq. (1)].



In some instances, at least, the cyclization can be carried out under very mild conditions.⁴² Treatment of α -aminoacetophenone hydrochloride, for example, with β -carbomethoxypropionyl chloride in the presence of pyridine gives methyl β -(5-phenyloxazole-2-yl) propionate (2).



A large number of 2- and 4-oxazolecarboxylic acid esters have been synthesized by this method using appropriate α -acylamino carbonyl compounds.^{27-30, 38, 40}

Wiegand and Rathburn⁴³ have recently reported that polyphosphoric acid cyclization of α -acetamido ketones gives 2,4,5-trialkyloxazoles in yields equal to or greater than those obtained with sulfuric acid. Japanese workers⁴⁴ claim that phosgene (COCl_2) in the presence of an organic base is another useful reagent to affect cyclization of suitably substituted

³⁹ E. Gustak, *Arh. Kem.* **24**, 15 (1952); *Chem. Abstr.* **49**, 296 (1955).

⁴⁰ G. Ya. Kondrat'eva and C.-H. Huang, *Zh. Obshch. Khim.* **32**, 2348 (1962); *J. Gen. Chem. USSR* **32**, 2315 (1962).

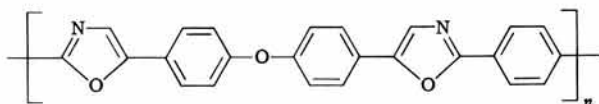
⁴¹ V. N. Kerr, F. N. Hayes, D. G. Ott, R. Lier, and E. Hansbury, *J. Org. Chem.* **24**, 1864 (1959).

⁴² John Wyeth and Brother Ltd., French Patent 1,587,052 (1970); *Chem. Abstr.* **74**, 53765 (1971).

⁴³ E. E. Wiegand and D. W. Rathburn, *Synthesis*, 648 (1970).

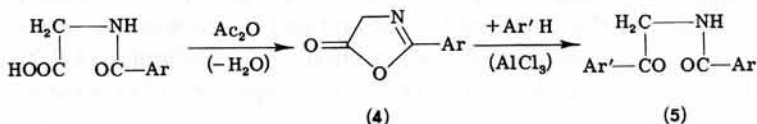
⁴⁴ R. Maeda, M. Takehara, and Y. Yoshida, Japanese Patent 34,422 (1971); *Chem. Abstr.* **76**, 3838 (1972).

α -acylamino carbonyl compounds to 2,4,5-trisubstituted oxazoles. Thermally stable poly(phenyleneoxazoles) (3) are obtained by thermal cyclodehydration of the corresponding polyamide precursor at 300° and 2 mm pressure.⁴⁵



(3)

One of the major problems encountered in this synthesis is the difficulty of obtaining the starting materials (either the α -aminocarbonyl compounds or their acylated derivatives). The former may be prepared by Neber rearrangement of ketoxime tosylates with a base such as ethoxide or pyridine.⁴⁶ α -Acylamino carbonyl compounds can be prepared directly by the reductive acetylation of oximino ketones.^{28,38} Balaban and his collaborators⁴⁷⁻⁵⁰ have developed an excellent method for the synthesis of α -acylamino ketones (5). They are obtained in yields of 50–90% by the reaction of azlactones (2-aryl-5-oxazolone, 4) with aromatic hydrocarbons in the presence of aluminum chloride under Friedel-Crafts conditions; the reaction may proceed either intermolecularly or intramolecularly.



(4)

(5)

Phosphorus oxychloride has been used for the cyclization of (5) to 2,5-diaryloxazoles.⁴⁷⁻⁵⁰

In a variation of this synthetic method 2-phenyl-2-oxazoline-5-one is treated with heterocyclic amines in refluxing tetrahydrofuran to give 6, which on cyclization gives the corresponding 5-heteroarylamino-2-phenyloxazole.⁵¹

⁴⁵ T. Shono, M. Hachihama, and K. Shinra, *J. Polym. Sci., Part B* **5**, 1001 (1967); *Chem. Abstr.* **67**, 117382 (1967).

⁴⁶ C. O'Brien, *Chem. Rev.* **64**, 81–89 (1964).

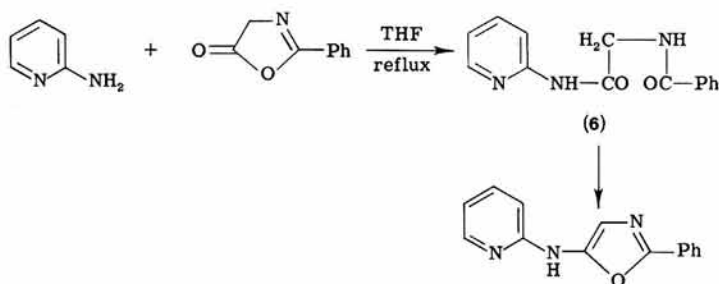
⁴⁷ P. T. Frangopol, A. T. Balaban, L. B. Birladeanu, and E. Ciorănescu, *Tetrahedron* **16**, 59 (1961).

⁴⁸ E. Ciorănescu, L. Birladeanu, P. T. Frangopol, and A. T. Balaban, *Rev. Chim., Acad. Rep. Populaire Roumaine* **7**, 755 (1962).

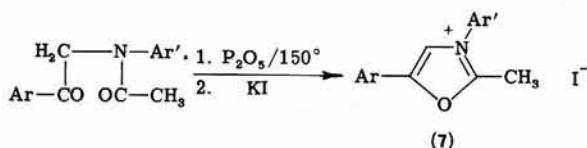
⁴⁹ A. T. Balaban, I. Bally, P. T. Frangopol, M. Bacescu, E. Ciorănescu, and L. Birladeanu, *Tetrahedron* **19**, 169 (1963).

⁵⁰ A. T. Balaban, L. Birladeanu, I. Bally, P. T. Frangopol, M. Mocanu, and Z. Simon, *Tetrahedron* **19**, 2199 (1963).

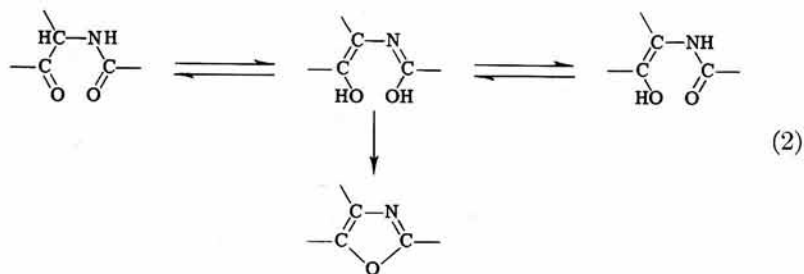
⁵¹ M. V. Strandtmann, U.S. Patent 3,624,097 (1971); *Chem. Abstr.* **76**, 59602 (1972).



3,5-Diaryloxazolium iodides (7) have been prepared⁵² by heating *N*-aryl-*N*-acetyl- α -aminoacetophenones with phosphorus pentoxide at 150° for 0.5 hour, and subsequent treatment of the product with potassium iodide.



Practically no effort has so far been made to study the mechanism of this synthesis. Cornforth, in his review,⁴ has suggested two possible routes for cyclization of the keto amides. Alberti and his co-workers³⁷ have supported the mechanism of transformation of α -acylamino ketones to oxazoles by the enolization of two carbonyl groups [Eq. (2)], a mechanism proposed by Wiley.¹

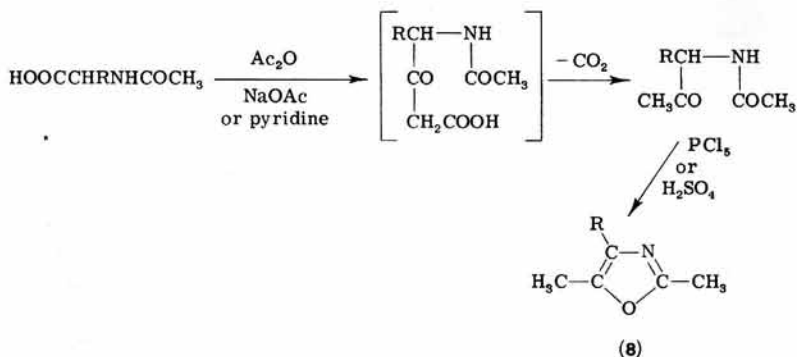


This mechanism, however, does not explain the exact nature of participation of the cyclodehydrating agents. It is also uncertain which of the two oxygen atoms is expelled on cyclization.

⁵² E. D. Sych and O. V. Moreiko, *Khim. Geterotsikl. Soedin.* **6**, 1034 (1970); *Chem. Abstr.* **74**, 143297 (1971).

B. FROM ACYL DERIVATIVES OF α -AMINO ACIDS

Heating an α -amino acid with acetic anhydride in the presence of sodium acetate or pyridine and subsequently treating the product with phosphorus pentachloride⁵³ or sulfuric acid⁵⁴ to give 4-substituted 2,5-dimethyloxazoles (**8**) is essentially the Wrede synthesis.⁵³ This procedure has not, however, found much practical utility as a synthetic method due to relatively poor yields of the oxazoles (about 15% generally, except in two cases where yields of over 50% have been reported).⁵⁴ At present there is no doubt that the first stage in this synthesis is a Dakin-West reaction producing an α -acetamido ketone which cyclizes readily in the second stage.



The decarboxylative acylation of α -aminophenylacetic acid in refluxing acetic anhydride alone gives about 20% yield of 2,5-dimethyl-4-phenyloxazole and a similar amount of uncyclized α -acetamido- α -phenylacetone.⁵⁵ 2-Vinyl- and 2-isopropenyl-4,5-dimethyloxazoles have been prepared in good yields by the Dakin-West reaction of *N*-acryloyl- and *N*-methacryloyl- α -alanine, respectively, followed by cyclization of the oxoamides in PPA at 140°C for 4 hours.^{56, 57}

⁵³ F. Wrede and G. Feuerriegel, *Z. Physiol. Chem.* **205**, 198 (1932); **218**, 129 (1933); F. Wrede, *ibid.* **206**, 146 (1932).

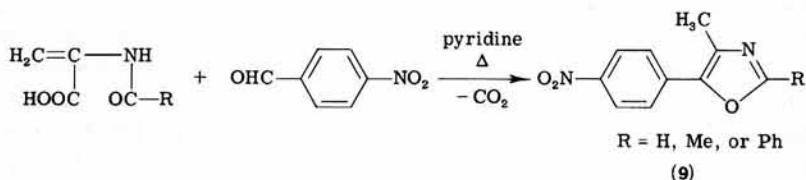
⁵⁴ R. H. Wiley, *J. Org. Chem.* **12**, 43 (1947).

⁵⁵ J. A. King and E. H. McMillan, *J. Amer. Chem. Soc.* **77**, 2814 (1955).

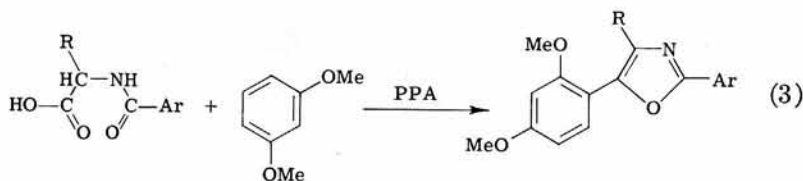
⁵⁶ Y. Iwakura, F. Toda, N. Kusakawa, and H. Suzuki, *J. Polym. Sci., Part B* **6**, 5 (1968); *Chem. Abstr.* **68**, 50147 (1968).

⁵⁷ Y. Iwakura, F. Toda, H. Suzuki, N. Kusakawa, and K. Yagi, *J. Polym. Sci., Part A-1* **10**, 1133 (1972); *Chem. Abstr.* **77**, 62340 (1972).

α -Acylaminoacrylic acids are decarboxylated in pyridine by heating on an oil bath with *p*-nitrobenzaldehyde to yield 2-substituted 4-methyl-5-(*p*-nitrophenyl)oxazoles (9) in 66–89% yields.⁵⁸ This reaction is different from the Wrede synthesis.⁵³



Alkoxybenzenes and -naphthalenes when treated at elevated temperatures with acylated α -amino acids in the presence of polyphosphoric acid react to give 2,4,5-trisubstituted oxazoles.⁵⁹ A typical reaction is illustrated in Eq. (3).



N-Benzoylalanine on fusion with phosphorus pentachloride yields, depending on the temperature, 2-phenyl-5-chloro-4-chloromethyl (or 4-dichloromethyl)oxazole in low yields (20–25%).⁶⁰

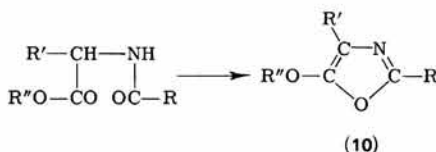
C. FROM ACYL DERIVATIVES OF α -AMINO ACID ESTERS (5-ALKOXYOXAZOLES)

The synthesis of 5-alkoxyoxazoles (10) from acylated α -amino acid esters is analogous to the cyclization of α -acylamino carbonyl compounds (1). The reactions are usually carried out in the presence of phosphorus pentachloride or pentoxide in chloroform solution.

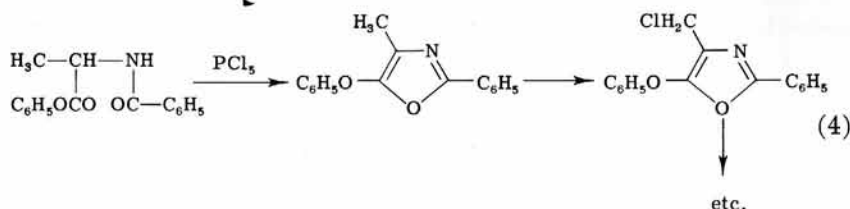
⁵⁸ S. Emoto and M. Ando, *J. Agr. Chem. Soc. Jap.* **35**, 1030 (1961); *Chem. Abstr.* **60**, 8121 (1964).

⁵⁹ P. Schlack and W. Koller, German Patent 1,109,690 (1958); *Chem. Abstr.* **56**, 8719 (1962).

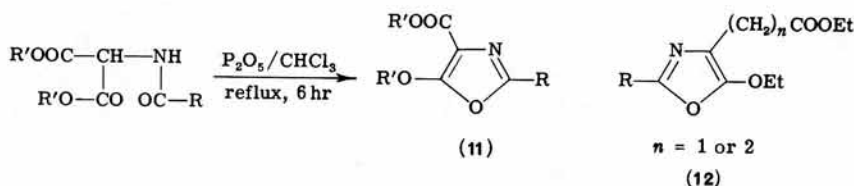
⁶⁰ T. Wieland, B. Hennig, and W. Loewe, *Chem. Ber.* **95**, 2232 (1962).



Subsequent developments, including cyclizations by means of benzenesulfonyl chloride or silver benzenesulfonate in pyridine, and by phosphoryl or thionyl chloride have already been reviewed by Cornforth.^{2,4} Of the above cyclodehydrating agents, phosphorus pentoxide is generally preferred to effect cyclizations smoothly,⁴⁰ for example, phosphorus pentachloride tends to give oxazoles chlorinated in the side chain,⁶⁰ as shown in Eq. (4).



Acylaminomalonic esters give 5-alkoxyoxazole-4-carboxylic esters (11) in 35–54% yield.^{61, 62} A number of (5-ethoxyoxazole-4-yl)-acetic and



-propionic acid esters (12, $n = 1$ or 2) have also been prepared by the application of this synthesis.⁶³

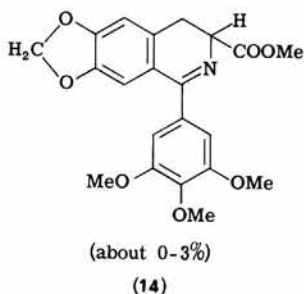
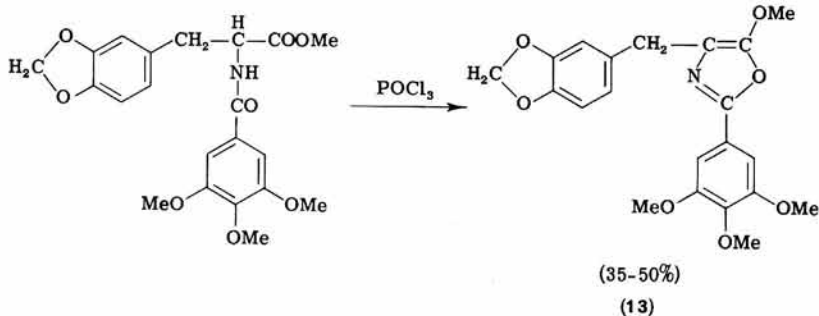
An interesting example of a competitive ring closure reaction yielding a 5-methoxyoxazole (13) in preference to the expected 3,4-dihydroisoquinoline derivative (14) has been reported by Reeve and Pare.⁶⁴

⁶¹ M. Grifantini and M. L. Stein, *Ann. Chim. (Rome)* **55**, 576 (1963); *Chem. Abstr.* **63**, 13234 (1965).

⁶² M. Grifantini, M. L. Stein, and A. Temperilli, *Ann. Chim. (Rome)* **56**, 946 (1966); *Chem. Abstr.* **66**, 37805 (1967).

⁶³ M. Kawazu, M. Seto, M. Watanabe, I. Wada, and E. Kaneko, Japanese Patent 43,383 (1971); *Chem. Abstr.* **76**, 59598 (1972).

⁶⁴ W. Reeve and P. J. Pare, *J. Amer. Chem. Soc.* **79**, 675 (1957).



The last decade has seen considerable interest, especially, in the synthesis of 4-methyl-5-alkoxyoxazoles (and related compounds)⁶⁵⁻⁷⁴ as they are valuable intermediates for the synthetic production of vitamin B₆ (pyridoxine) and its analogs, through Diels-Alder reaction with suitable dienophiles^{65, 68-70, 73} (see Section IV, D). Alkyl *N*-formylalaninates (15)

⁶⁵ E. E. Harris, R. A. Firestone, K. Pfister, R. R. Boettcher, F. J. Cross, R. B. Currie, M. Monaco, E. R. Peterson, and W. Reuter, *J. Org. Chem.* **27**, 2705 (1962).

⁶⁶ K. Pfister and E. E. Harris, Belgian Patent 617,499 (1962); *Chem. Abstr.* **59**, 634 (1963).

⁶⁷ F. Hoffmann-La Roche & Co., A.-G., Netherlands Patent Appl. 6,508,673 (1966); *Chem. Abstr.* **64**, 14193 (1966).

⁶⁸ K. Pfister, E. E. Harris, and R. A. Firestone, U.S. Patent 3,227,721 (1966); *Chem. Abstr.* **64**, 9689 (1966).

⁶⁹ R. A. Firestone, E. E. Harris, and W. Reuter, *Tetrahedron* **23**, 943 (1967).

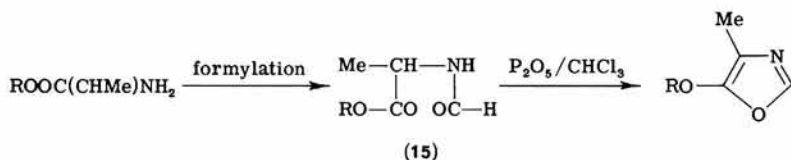
⁷⁰ P. F. Mühlradt, Y. Morino, and E. E. Snell, *J. Med. Chem.* **10**, 341 (1967).

⁷¹ S. Asai and R. Yoshida, Japanese Patent 18,773 (1968); *Chem. Abstr.* **70**, 68346 (1969).

⁷² S. Asai and R. Yoshida, Japanese Patent 18,772 (1968); *Chem. Abstr.* **70**, 77940 (1969).

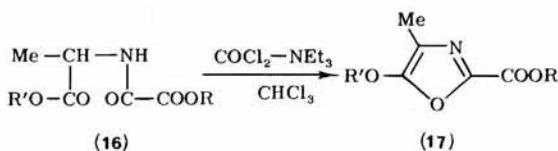
⁷³ M. V. Balyakina, Z. N. Zhukova, and E. S. Zhdanovich, *Zh. Prikl. Khim. (Leningrad)* **41**, 2324 (1968); *Chem. Abstr.* **70**, 68074 (1969).

⁷⁴ T. Naito, Y. Morita, S. Onishi, and I. Tabara, Japanese Patent 30,816 (1970); *Chem. Abstr.* **74**, 42347 (1971).

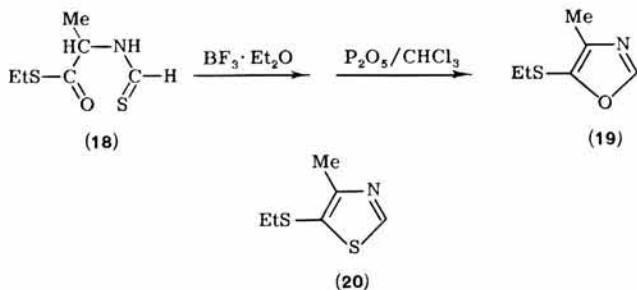


(obtained by the formylation of alkyl alaninates with formic-acetic anhydride,⁶⁵ formamide,⁶⁸ or ethyl formate)⁷³ have exclusively been cyclized in chloroform solutions using phosphorus pentoxide as the dehydrating agent or in conjunction with some added catalysts or diluents such as boron trifluoride etherate,⁶⁷ metal oxides (alumina⁷¹ or magnesium oxide),⁷⁴ or tributyl phosphate.⁷² The product is isolated either by ether extraction or steam distillation of the aqueous alkali-treated reaction mixture. In general, yields of 50% and over, sometimes almost quantitative, have been reported.

Japanese workers⁷⁵ claim the superiority of a phosgene-triethylamine mixture (ratio 1:2) over other conventional dehydrating agents. Thus, they devised a novel synthesis of 4-methyl-5-alkoxyoxazole-2-carboxylic acid esters (17) by condensation of alkyl alaninate hydrochloride with diethyl or dimethyl oxalate followed by cyclization of the product (16).



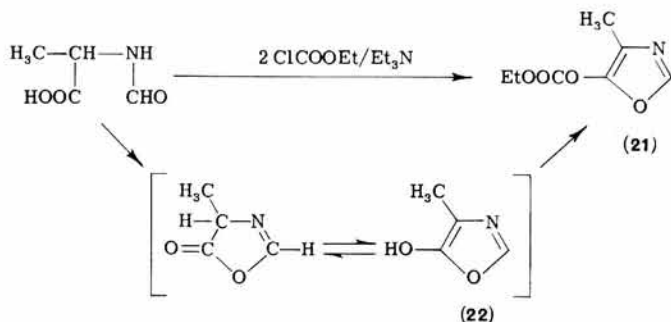
An interesting variant is the preparation of 4-methyl-(5-ethylthio)-oxazole (19), a potential intermediate for the synthesis of vitamin B₆, from *N*-(formylthio)alanine *S*-ethyl ester (18) under the influence of



⁷⁵ I. Maeda, M. Takehara, K. Togo, S. Asai, and R. Yoshida, *Bull. Chem. Soc. Jap.* **42**, 1435 (1969).

boron trifluoride, followed by refluxing the syrupy complex product with phosphorus pentoxide in chloroform.⁷⁶ Possibly, the corresponding thiazole derivative (20) is not formed in appreciable amounts, as almost quantitative yield of the oxazole (19) has been reported.

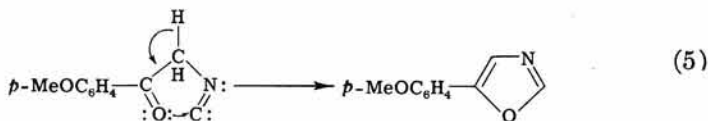
Another modification by Japanese workers⁷⁷ is reminiscent of both this and the preceding synthetic method as far as the starting material is concerned. Interaction of *N*-formylalanine with ethyl chloroformate in the presence of triethylamine at -10 to -20° affords an 80% yield of 4-methyl-5-ethoxycarbonyloxazole (21). The reaction has been



suggested to occur through the enol (22) of 4-methyl-2-oxazolin-5-one. In fact, 2-methyl-4-benzyl-2-oxazolin-5-one does react with ethyl chloroformate to give 2-methyl-4-benzyl-5-ethoxycarbonyloxazole.⁷⁷

D. FROM α -ISOCYANO CARBONYL COMPOUNDS

An isolated example of the cycloisomerization of a β -keto isocyanide to an oxazole derivative is the ready cyclization [Eq. (5)] of *p*-methoxybenzoylmethyl isonitrile on warming in neutral medium to give a practically quantitative yield of 5-*p*-methoxyphenyloxazole.⁷⁸

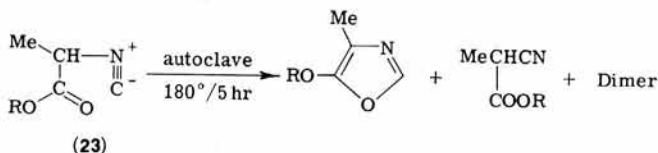


⁷⁶ T. Naito, K. Ueno, and T. Miki, Japanese Patent 23,088 (1969); *Chem. Abstr.* **71**, 124405 (1969).

⁷⁷ M. Murakami and M. Iwanami, *Bull. Chem. Soc. Jap.* **41**, 726 (1968).

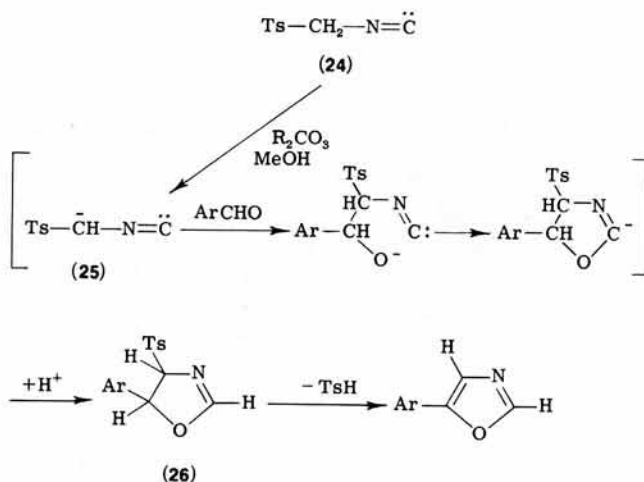
⁷⁸ I. Hagedorn, U. Eholzer, and H. D. Winkelmann, *Angew. Chem. Int. Ed. Engl.* **3**, 647 (1964); I. Hagedorn, U. Eholzer, and H. Etling, *Chem. Ber.* **98**, 193 (1965).

In 1968 Japanese workers⁷⁹ filed a patent application in which was described the preparation of 4-methyl-5-alkoxyoxazoles by thermal cyclization of lower alkyl esters of (α -isocyano)alkylcarboxylic acids (**23**). This application, followed by a detailed paper, claims a yield of 20–40% of the oxazole, accompanied by some other products such as the isomeric cyanide and its dimer. The mechanism of this reaction is uncertain, but



it is believed to occur through the abstraction of the α -hydrogen of the isonitrile (**23**).⁸⁰ This method deserves further investigation.

Recently, a novel and efficient synthesis of oxazoles from tosylmethyl isocyanide and carbonyl compounds has been discovered by van Leusen *et al.*⁸¹ Thus, 5-aryloxazoles are prepared in 57–91% yield by refluxing tosylmethyl isocyanide (**24**) and aromatic aldehydes in methanol in the presence of potassium carbonate.



Apparently the reaction takes place by the nucleophilic attack of

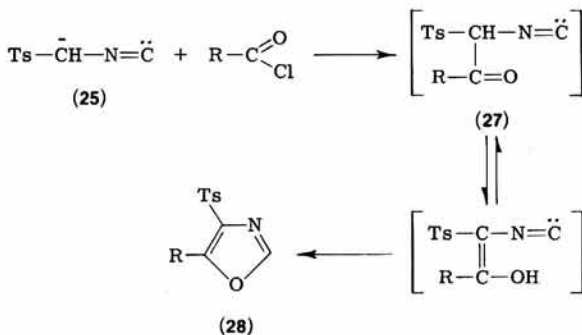
⁷⁹ I. Maeda, S. Asai, and R. Yoshida, Japanese Patent 19,953 (1968); *Chem. Abstr.* **70**, 68347 (1969).

⁸⁰ I. Maeda, K. Togo, and R. Yoshida, *Bull. Chem. Soc. Jap.* **44**, 1407 (1971).

⁸¹ A. M. van Leusen, B. E. Hoogenboom, and H. Siderius, *Tetrahedron Lett.*, 2369 (1972).

tosylmethyl isocyanide anion (25) on the aldehyde, followed by ring closure and elimination of *p*-toluenesulfonic acid. The intermediate 4-tosyl- Δ^2 -oxazolines (26) may be isolated at lower reaction temperatures (e.g., at 20°C).⁸¹

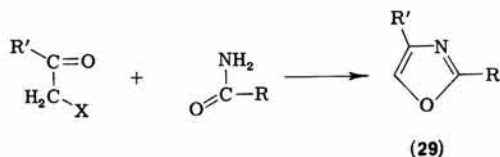
The replacement of acid chlorides or anhydrides for the aldehyde component offers a route to oxazoles (28) with a tosyl substituent in the 4-position. The reaction is presumed⁸¹ to occur via the acyl derivatives (27), which, however, have not been isolated. But, nevertheless, the



intermediate (27) is analogous to a β -keto isonitrile which is known to cycloisomerize to give an oxazole.⁷⁸

E. FROM α -HALO CARBONYL COMPOUNDS AND AMIDES

The synthesis of Blümlein⁸² and Lewy,⁸³ which affords moderate yields of 2,4-disubstituted oxazoles (29) (having at least one aryl group) by the condensation of α -halo ketones with amides (other than formamide) is even at present a method of choice because of the ready availability of the starting materials. It has been extensively applied to the preparation of many 2,4-disubstituted oxazoles^{20, 21, 40, 84-86} and is equally applicable



⁸² F. O. Blümlein, *Ber.* **17**, 2578 (1884).

⁸³ M. Lewy, *Ber.* **20**, 2576 (1887); **21**, 924, 2192 (1888).

⁸⁴ G. Theilig, *Chem. Ber.* **86**, 96 (1953).

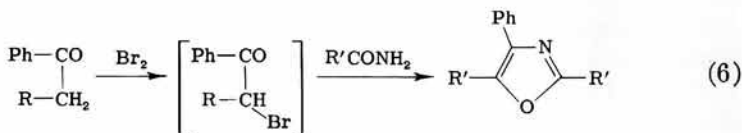
⁸⁵ I. Simiti and E. Chindris, *Arch. Pharm. (Weinheim)* **304**, 425 (1971).

⁸⁶ D. M. O'Mant, *British Amended* 1,139,940 (1969); *Chem. Abstr.* **75**, 140825 (1971).

when a trisubstituted oxazole is required. The reaction is usually carried out by heating the reactants together at or above 110°.

In the case of lower alkyl amides the components are heated in a high-boiling inert solvent such as xylene or dimethylformamide.^{87,88} Ethyl α -chloroacetoacetate reacts with benzamide at 180° to give a very poor yield of ethyl 2-phenyl-4-methyloxazole-5-carboxylate.²⁷

Perhaps the simplest method of oxazole synthesis would involve bromination of a ketone in the presence of an amide as shown in Eq. (6), that is, generating the required α -bromo ketone *in situ*. Marquez⁸⁹ thus prepared several 4-phenyl 2,5-disubstituted oxazoles by adding calculated amounts of bromine to a heated mixture of ketone and amide. With unsymmetrical



ketones, where bromination at two sites is possible, a mixture of two isomeric oxazoles would be expected.

This method has afforded some 2-phenyl-4-(β -aminoethyl)-, and 2-phenyl-4-(β -disubstituted-aminoethyl)oxazoles from benzamide and the appropriate substituted bromobutanones.⁹⁰ A 5-oxazolylethanol derivative is obtained from the corresponding substituted α -chloro ketone and amide in the presence of calcium carbonate (to neutralize the generated hydrogen chloride.)⁹¹ Condensation of α -bromophenylacetaldehyde and *p*-bromobenzamide at 110°–120° gives 50% yield of 2-*p*-bromophenyl-5-phenyloxazole.¹⁸

Probably the most valuable advance in the field of oxazole syntheses has come from the methods developed by Brederick and his co-workers.^{92–94} The so-called "formamide synthesis" of Brederick *et al.* involves, especially in this case, the interaction of α -halo ketones with formamide and usually results in high yields of oxazoles (50–70%).

Although reviews dealing with general syntheses involving formamide

⁸⁷ J. Haginiwa, *J. Pharm. Soc. Jap.* **73**, 1310 (1953); *Chem. Abstr.* **49**, 298 (1955).

⁸⁸ I. Saikawa and S. Takano, Japanese Patent 21,866 (1971); *Chem. Abstr.* **75**, 76773 (1971).

⁸⁹ F. Marquez, *An. Real Soc. Espan. Fis. Quim. Ser. B* **57**, 723 (1961); *Chem. Abstr.* **57**, 12467 (1962).

⁹⁰ M. Tavelia, *Ann. Chim. (Rome)* **53**, 488 (1963); *Chem. Abstr.* **59**, 7507 (1963).

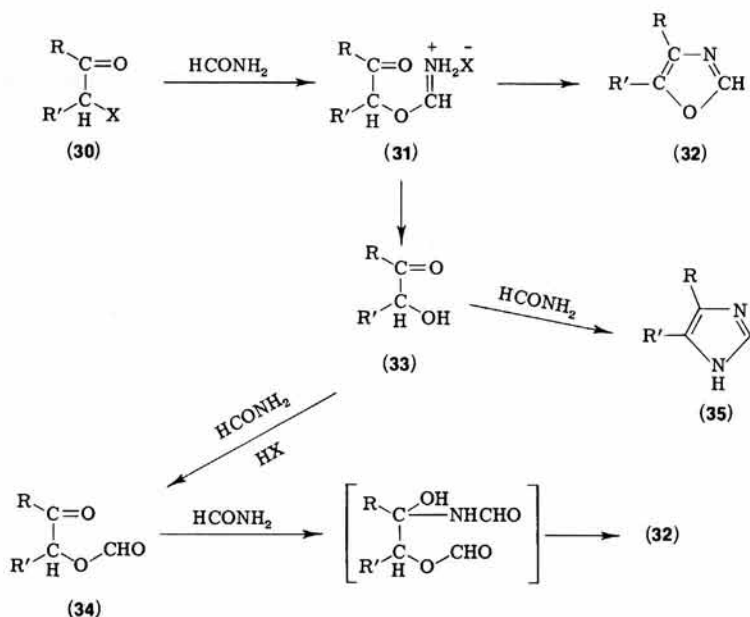
⁹¹ U. H. Lindberg, J. Pedersen, and B. Ulff, *Acta Pharm. Suecica* **4**, 269 (1967).

⁹² H. Brederick and G. Theilig, *Chem. Ber.* **86**, 88 (1953).

⁹³ H. Brederick and R. Gompper, *Chem. Ber.* **87**, 700 (1954).

⁹⁴ H. Brederick and R. Gompper, *Chem. Ber.* **87**, 726 (1954).

and other acid amides have already appeared,^{10,95} a summary of the work pertaining to oxazole synthesis is desirable at this stage. The general reaction can be formulated as in Scheme 1.



Scheme 1

Initially α -halo ketones (30) react with formamide to give iminoesters (31), which then either ring-close to the oxazoles (32) or decompose to form α -hydroxy ketones (33). The α -hydroxy ketones formed in this way react with excess formamide in the presence of liberated hydrogen halides or the added quantity of sulfuric acid to give α -formoxy ketones (34) which then yield the oxazoles (32) with formamide.^{10,95} On the other hand, α -hydroxy ketones and formamide in the absence of added sulfuric acid yield imidazoles (35) predominantly.⁹² Evidence for this reaction pathway came from the observations that α -formoxy ketones could be isolated, and reaction with formamide converted them into the oxazoles.⁹⁴

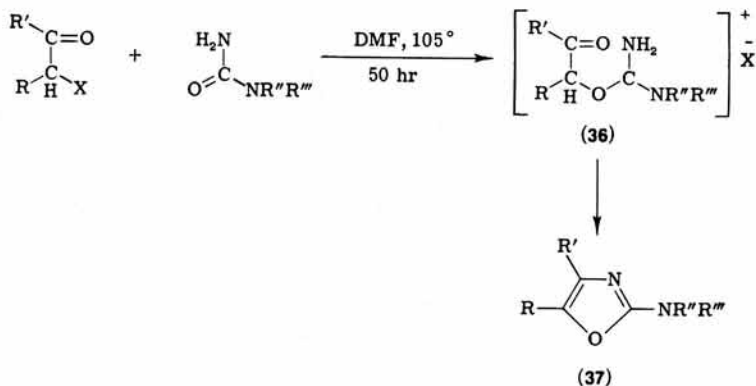
The formation of oxazoles generally predominates at around 130° when slightly more than a molar quantity of formamide is used. At higher temperatures (180°–200°C) and with a large excess of formamide, the

⁹⁵ H. Brederick, R. Gompper, H. G. von Schuh, and G. Theilig, *Angew. Chem.* **71**, 753–774 (1959).

imidazole ring is formed preferentially.⁸⁴ Acetals of higher α -bromoaldehydes and formamide yield monosubstituted imidazoles and oxazoles.⁹⁶ The oxazole synthesis is about equally successful when α -halo ketones are boiled with a mixture of ammonium formate and formic acid (large excess) in place of formamide and concentrated sulfuric acid.⁹³ Lindberg *et al.*⁹⁷⁻¹⁰⁰ have used either polyphosphoric acid or sulfuric acid with formamide to prepare a number of 2-unsubstituted oxazoles including 5-oxazolyethanol and 5-oxazolylmethanol derivatives.

The ammonium formate in formic acid procedure has rendered possible the first preparation of isomeric 4,5-disubstituted oxazoles.^{93,101} Bredereck, Gompper, and Reich¹⁰¹ have reported the anomalous behavior of certain long-chain α -bromo ketones: a single α -bromo ketone on reaction with ammonium formate in formic acid gives a mixture of two isomeric oxazoles. Refluxing of α -bromo ketones or of α -chloro- β -keto esters with ammonium acetate in acetic acid results in the formation of substituted 2-methyloxazoles.^{40,102} Ethyl α -chloroacetoacetate on heating with ammonium carbonate or formamide in formic acid yields 4-methyloxazole-5-carboxylic ester.^{40,103}

In a reaction analogous to the synthesis of 2-aminothiazoles from



⁹⁶ H. Bredereck, R. Gompper, R. Bangert, and H. Herlinger, *Angew. Chem.* **70**, 269 (1958).

⁹⁷ U. H. Lindberg, *Acta Pharm. Suecica* **3**, 161 (1966).

⁹⁸ U. H. Lindberg, G. Bexell, J. Pedersen, and S. Ross, *Acta Pharm. Suecica* **7**, 423 (1970).

⁹⁹ U. H. Lindberg, *Acta Pharm. Suecica* **8**, 39 (1971).

¹⁰⁰ U. H. Lindberg, G. Bexell, and B. Ulff, *Acta Pharm. Suecica* **8**, 49 (1971).

¹⁰¹ H. Bredereck, R. Gompper, and F. Reich, *Chem. Ber.* **93**, 723 (1960).

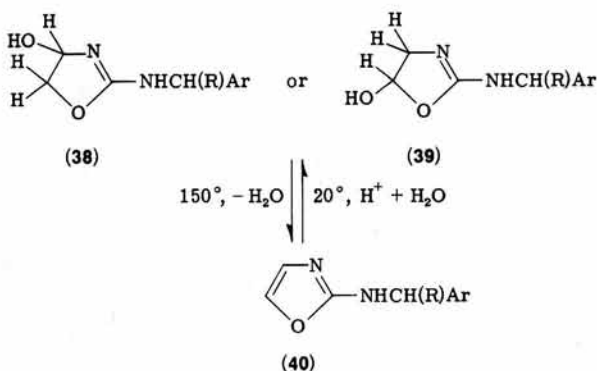
¹⁰² H. Bredereck, R. Gompper, and F. Reich, *Chem. Ber.* **93**, 1389 (1960).

¹⁰³ A. Dornow and H. Hell, *Chem. Ber.* **94**, 1248 (1961).

α -halo ketones and thioureas, Gompper and Christmann¹⁰⁴ found that α -halo ketones condense with urea, N-mono-, and N,N-disubstituted ureas in dimethylformamide (DMF) solution to yield the corresponding 2-aminooxazoles (37).^{100, 104-107} The mechanism of the reaction is uncertain, but is believed to proceed through the intermediate (36).

Generally the yields of 2-aminooxazoles (37) are moderate to good; with 2-amino-4,5-diphenyloxazole maximum yield of 91% has been obtained. Poor yields of the oxazoles are often accompanied by the formation of imidazoles and 2-imidazolones as by-products.¹⁰⁴

Najer, Giudicelli, and Menin¹⁰⁸ have used the method to prepare a number of substituted 2-aminooxazoles, e.g., 4,5-tetramethylene- and 4,5-pentamethylene-2-aminooxazole from the corresponding α -bromocycloalkanones and urea. Bromoacetaldehyde reacts with urea, and alkyl- and arylureas to give 2-amino-, 2-alkylamino-, and 2-arylaminooxazoles, while aralkylureas behave differently to give 4 (or 5)-hydroxy-2-oxazoline derivatives (38, 39).¹⁰⁹ These 2-aralkylamino-4-hydroxy- or -5-hydroxy-2-oxazolines (38 and 39, respectively) lose a molecule of water when heated at 150° to form the corresponding oxazoles (40), which have a peculiar property of adding, in dilute hydrochloric acid in the cold, 1 mole of water at position- 4,5 to give back 38 and/or 39.



α -Bromopropionaldehyde and -butyraldehyde when refluxed in methanol

¹⁰⁴ R. Gompper and O. Christmann, *Chem. Ber.* **92**, 1944 (1959).

¹⁰⁵ R. Gompper and O. Christmann, German Patent 1,092,920 (1960); *Chem. Abstr.* **55**, 19951 (1961).

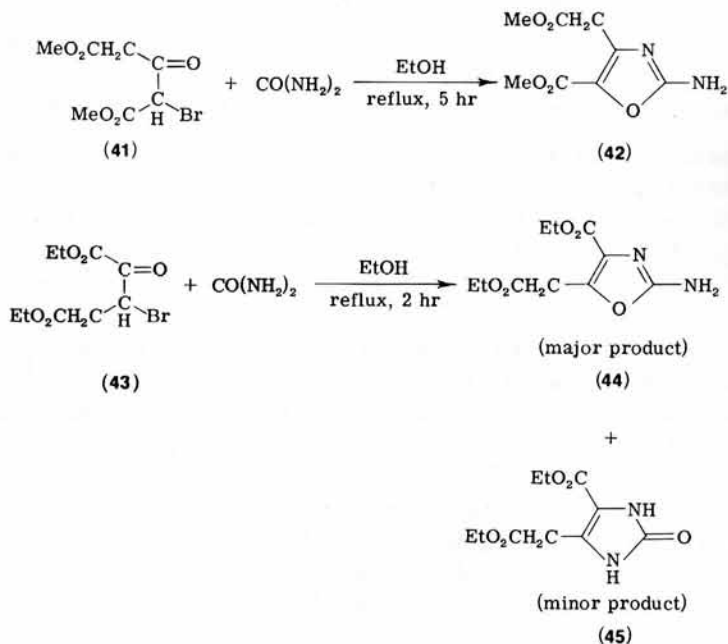
¹⁰⁶ Instituto Farmacologico Sersono S.p.A., French Medicinal Patent 7043 (1969); *Chem. Abstr.* **74**, 100024 (1971).

¹⁰⁷ C. Tanaka and H. Shibakawa, *Yakugaku Zasshi* **91**, 425 (1971).

¹⁰⁸ H. Najer, R. Giudicelli, and J. Menin, *Bull. Soc. Chim. Fr.*, 2040 (1967).

¹⁰⁹ H. Najer, R. Giudicelli, and J. Menin, *Bull. Soc. Chim. Fr.*, 2052 (1960).

for 24 hours with urea give 5-methyl- and 5-ethyl-2-aminooxazole, respectively.¹¹⁰ The preparation of oxazoles from α -halo- β -keto esters has also been reported. Japanese workers have prepared methyl 2-amino-5-carbomethoxy-4-oxazolylacetate (42) and ethyl 2-amino-4-ethoxycarbonyl-5-oxazolylacetate (44) by refluxing dimethyl 2-bromo-3-oxoglutarate (41) and diethyl 3-bromo-2-oxoglutarate (43), respectively, with urea in ethanolic medium.^{111, 112} Ethyl 4-ethoxycarbonyl-2-(3*H*)-imidazolone-5-



acetate (45) is obtained as a minor by-product in the latter reaction.

The reaction between ω -bromoacetophenone or its *p*-substituted derivatives and cyanourea is dependent on pH and gives either an imidazole or an oxazole derivative, depending on the conditions.¹¹³ Thus, equimolar amounts of ω -bromoacetophenones and cyanourea in the presence of 2.5–3 M sodium acetate in ethanolic medium give 30–50% yield of the corresponding 2-amino-5-aryloxazole (47). The mechanism of the reaction is uncertain, but it is believed to proceed through the anion of cyanourea

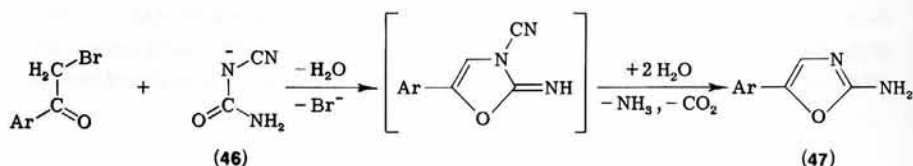
¹¹⁰ V. Wolf, P. Hauschildt, and W. Loop, *Chem. Ber.* **95**, 2419 (1962).

¹¹¹ I. Ito, S. Murakami, and K. Tanabe, *Yakugaku Zasshi* **86**, 300 (1966); *Chem. Abstr.* **65**, 3852 (1966).

¹¹² I. Kumashiro, *Nippon Kagaku Zasshi* **82**, 928 (1961); *Chem. Abstr.* **57**, 11183 (1962).

¹¹³ H. Beyer and H. Schilling, *Z. Chem.* **5**, 182 (1965); *Chem. Ber.* **99**, 2110 (1966).

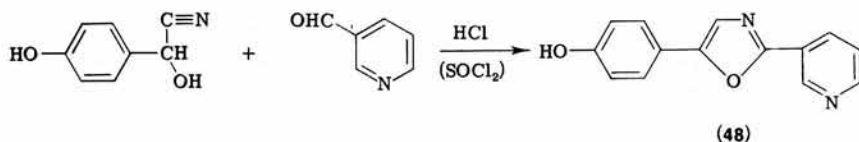
(46). This reaction is different from that of Gompper and Christmann¹⁰⁴ inasmuch as the latter gives 2-amino-4-aryloxazole from the reaction of ω -bromoacetophenones and urea.



F. FROM CYANOHYDRINS AND ALDEHYDES (FISCHER OXAZOLE SYNTHESIS)

Saturation of an equimolar mixture of aromatic aldehyde cyanohydrins and aromatic aldehydes in absolute ether at 0°C with dry hydrogen chloride results in the formation of 2,5-diaryloxazoles.^{114,115} The reaction often yields 2,5-diaryl-4-oxazolidones as by-products, and oxazolid-4-ones are the only products or major by-products if either of the starting materials is aliphatic.

Balaban and Frangopol¹¹⁶ observed that the addition of thionyl chloride precludes the formation of oxazolid-4-one and that the yield of 2,5-diphenyloxazole (PPO) is a function of the amount of added thionyl chloride. Some patents^{20,21} have described the preparation of hitherto unknown 2,5-diaryloxazoles with amino and dialkylamino substituents at the para position of the benzene ring, for use as photoconductive materials for electrophotography. Recently the reaction has been applied for the one-step synthesis of halfordinol (48), an oxazole alkaloid, from *p*-hydroxymandelonitrile and nicotinaldehyde.¹¹⁷



Although several attempts have been made to explain the formation of the oxazoles and oxazolidones from a common intermediate (previously reviewed),^{1,4} the mechanism of the reaction is not yet completely understood. Further, the synthesis is not unambiguous as it may give a mixture

¹¹⁴ E. Fischer, *Ber.* **29**, 205 (1896).

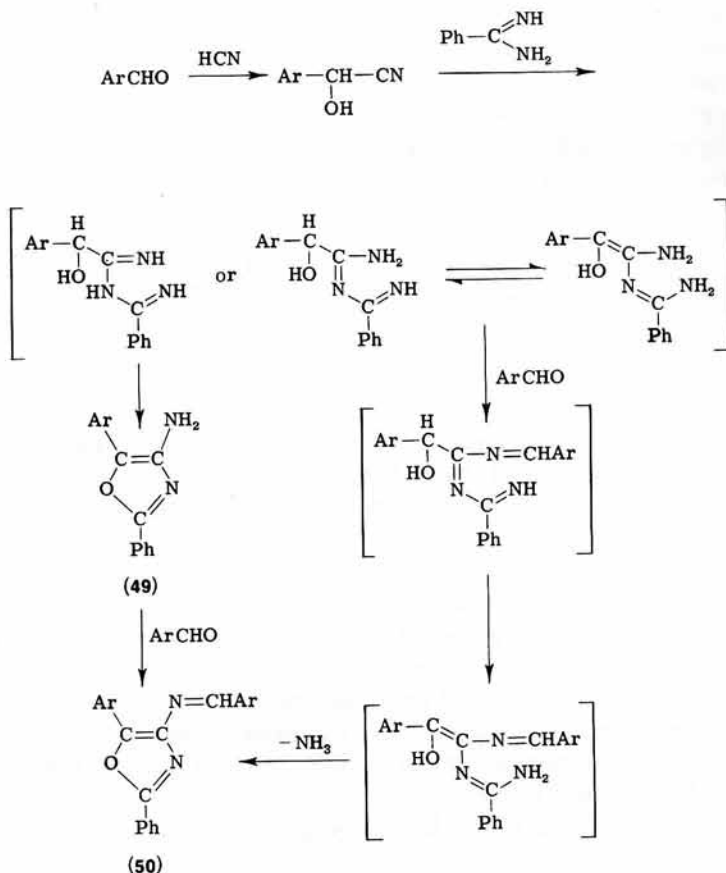
¹¹⁵ M. Ionescu and C. Makkay, *Stud. Univ. Babes-Bolyai, Ser. Chem.* **8**, 283 (1963).

¹¹⁶ A. T. Balaban and P. Frangopol, *Acad. Rep. Pop. Rom., Stud. Cercet. Chim.* **6**, 427 (1958); *Chem. Abstr.* **53**, 16112 (1959).

¹¹⁷ T. Onaka, *Tetrahedron Lett.*, 4393 (1971).

of oxazole bases when the cyanohydrin is not derived from the aldehyde employed.

A somewhat related reaction utilizing cyanohydrin precursors and benzamidine affords 4-aminooxazole derivatives.¹¹⁸ Thus benzamidine reacts with aromatic aldehydes in the presence of hydrogen cyanide in aqueous methanol, forming 4-arylmethylidenamino-2-phenyl-5-aryloxazoles (50). A tentative reaction mechanism has been proposed for this reaction (Scheme 2), but without supporting evidence.¹¹⁸ It is doubtful



Scheme 2

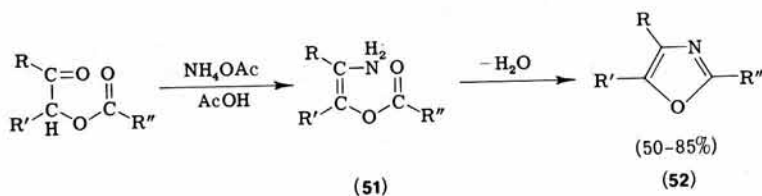
whether the 4-aminooxazole derivative (49) is a true intermediate unless it is isolated. Once again, like the Fischer synthesis, aliphatic aldehydes

¹¹⁸ E. Haruki, H. Imanaka, and E. Imoto, *Bull. Chem. Soc. Jap.* **41**, 1368 (1968).

fail to give oxazoles; α -hydroxyalkyldiphenyl-*s*-triazines are isolated. However, under the same reaction conditions *m*-nitrobenzaldehyde gives dimethyl azoxybenzene-3,3'-dicarboxylate.¹¹⁸ The mechanism of their formation is not considered here as it is beyond the scope of this review.

G. FROM ACYL DERIVATIVES OF α -HYDROXY KETONES

The observation by Davidson, Weiss, and Jelling¹¹⁹ that acyl derivatives of benzoin react with ammonium acetate in glacial acetic acid to give excellent yields of 2-substituted 4,5-diphenyloxazole opened a new era in the synthesis of oxazoles. This method enabled Theilig⁸⁴ and others¹²⁰⁻¹²² to prepare a series of otherwise inaccessible trisubstituted oxazoles (**52**), generally in high yields, by boiling the esters of aliphatic or mixed aliphatic-aromatic acyloins and carboxylic acids in acetic acid-ammonium acetate.



The reaction has been suggested¹²² to occur through enamine intermediates (**51**) and indeed, these have been prepared by other methods and converted into the oxazole derivatives by boiling in glacial acetic acid.¹²³

Conventionally the acyl derivatives of acyloins and benzoin esters may readily be obtained by reaction with acid anhydrides. The acyloin esters can more conveniently be prepared by allowing the corresponding α -bromo ketones and the sodium or potassium salts of the appropriate carboxylic acid to react, either in ethanol or in the acid to be esterified. The esters may not necessarily be isolated, and the oxazoles are obtained directly by adding the ammonium salt to, or passing ammonia through, the mixture, which is then boiled.⁸⁴ The reaction then becomes useful for the preparation of oxazoles (**53**) from α -bromo ketones and carboxylic acids.^{84, 121}

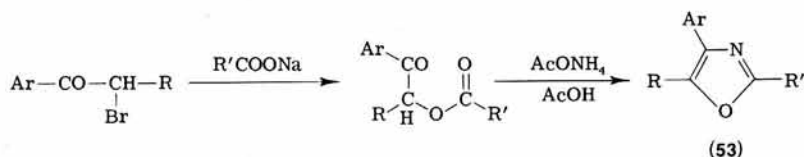
¹¹⁹ D. Davidson, M. Weiss, and M. Jelling, *J. Org. Chem.* **2**, 328 (1937).

¹²⁰ H. Bredereck, R. Gompper, and H. Wild, *Chem. Ber.* **88**, 1351 (1955).

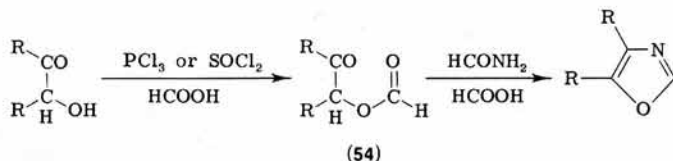
¹²¹ D. L. Aldous, J. L. Riebsomer, and R. N. Castle, *J. Org. Chem.* **25**, 1151 (1960).

¹²² P. P. E. Strzybny, T. van Es, and O. G. Backeberg, *J. Org. Chem.* **28**, 3381 (1963).

¹²³ H. J. Jakobsen, E. H. Larsen, P. Madsen, and S.-O. Lawesson, *Ark. Kemi* **24**, 519 (1965).



This method is not suited to the preparation of 2-unsubstituted oxazoles; the main difficulty is the preparation of the acyloin formates themselves. Bredereck and Gompper⁹⁴ introduced a new method of synthesizing the acyloin formates (54) by the treatment of acyloins in formic acid solution in the cold with either phosphorus trichloride or thionyl chloride. The yields in the three reported cases are 61–91%. These α -formyloxy ketones on boiling with formamide in formic acid afford the corresponding oxazoles, unsubstituted in the 2-position, in 61–75% yields.⁹⁴

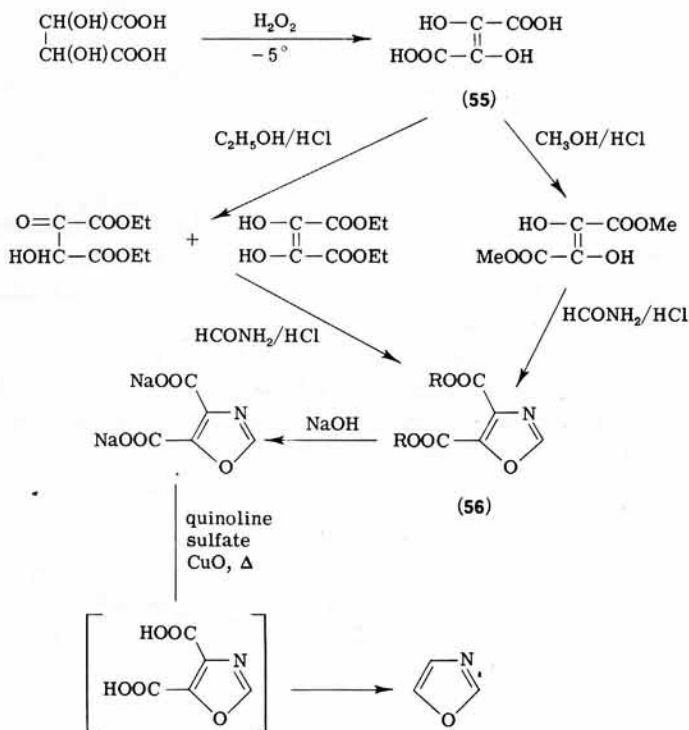


In a variation⁹⁴ of this procedure, acyloins themselves have been converted directly into 2-unsubstituted oxazoles by reaction with formamide and concentrated sulfuric acid at 100°–150°. The yields in this case, compared to overall yields of the two stages of the previous method, are either nearly the same or better.

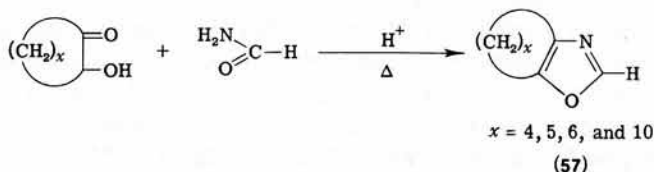
An interesting application of this method is a convenient synthesis of the parent oxazole.^{124,125} It is prepared by oxidizing tartaric acid with hydrogen peroxide to dihydroxyfumaric acid (55), the methyl or ethyl ester of which is condensed with formamide in the presence of hydrogen chloride to give 4,5-dialkoxycarbonyloxazole (56, R = Me or Et), which is saponified with aqueous barium hydroxide or alcoholic sodium hydroxide. The anhydrous salt is then decarboxylated to oxazole, without isolation of the comparatively unstable 4,5-oxazoledicarboxylic acid, in 55–70% yield.

¹²⁴ H. Bredereck and R. Bangert, *Angew. Chem.* **74**, 905 (1962); *Angew. Chem. Int. Ed. Engl.* **1**, 662 (1962).

¹²⁵ H. Bredereck and R. Bangert, *Chem. Ber.* **97**, 1414 (1964).



Further, the fused-ring oxazoles (57) are readily prepared from the corresponding cyclic acyloins by condensation with formamide in acidic medium.^{94, 126}

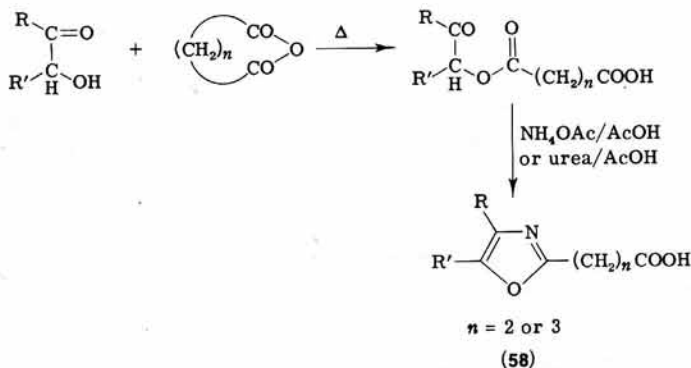


Several recent patents^{42, 127, 128} describe the preparation of 4,5-disubstituted oxazole-2-yl alcanoic acids (58) by the reaction of an α -ketol ester with urea in acetic acid or by acetylation of an α -ketol with a cyclic anhydride followed by refluxing with ammonium acetate in acetic acid.

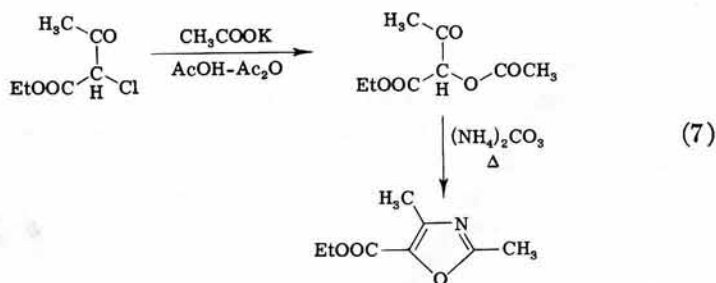
¹²⁶ H. H. Wasserman and E. Druckrey, *J. Amer. Chem. Soc.* **90**, 2440 (1968).

¹²⁷ K. Brown, British Patent 1,206,403 (1970); *Chem. Abstr.* **74**, 22814 (1971).

¹²⁸ K. Brown, U.S. Patent 3,578,671 (1971); *Chem. Abstr.* **75**, 36005 (1971).



α -Acyloxy- β -keto esters under these conditions give oxazolyl-5-carboxylic esters. The yields are often poor to moderate.^{122, 129-131} Kondrat'eva and Huang,⁴⁰ however, have obtained ethyl 2,4-dimethyloxazole-5-carboxylate in over 40% yield by heating ethyl α -chloroacetoacetate with potassium acetate in acetic acid-acetic anhydride at 110°, followed by heating with ammonium carbonate [Eq. (7)]. By analogy from above, the first step in this reaction is the replacement of chlorine by acetoxy.



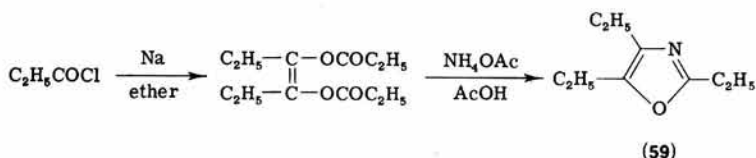
Another variation of this oxazole synthesis consists in the utilization of diesters of enediols (diacyl derivatives of the enol tautomer of α -hydroxy ketones). In the aliphatic series, enediol esters can directly be prepared from acyl chlorides and metallic sodium in ether containing a trace of water. When the esters react with ammonium acetate, symmetrical

¹²⁹ J. W. Cornforth and R. H. Cornforth, *J. Chem. Soc.*, 93 (1953).

¹³⁰ N. Saito and C. Tanaka, *J. Pharm. Soc. Jap.* **76**, 307 (1956); *Chem. Abstr.* **50**, 13874 (1956).

¹³¹ C. Tanaka and N. Saito, *Yakugaku Zasshi* **82**, 140 (1962); *Chem. Abstr.* **58**, 3407 (1963).

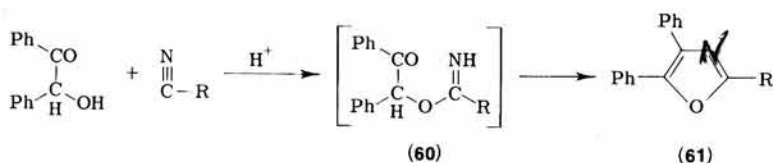
trialkylloxazoles (59) are formed.⁸⁴ The formation of oxazole probably



results via the initial removal of one ester group, followed by the conversion of the acyloin ester produced into the oxazole by means of ammonia.

H. FROM α -HYDROXY KETONES AND NITRILES

The reaction between benzoin and nitriles (including hydrogen cyanide) in the presence of concentrated sulfuric acid to give moderate yields of 4,5-diphenyloxazoles (61) was discovered by Japp and Murray¹³² in 1893, and possibly proceeds via an imino ether (60).



Further synthetic potential of the reaction was completely unexplored for about 70 years until the 1960s, when a number of patents^{20,21} claimed the synthesis of the 4,5-diaryloxazoles by condensation of benzoin with hydrocyanic acid or with aliphatic nitriles, using sulfuric or polyphosphoric acid as the condensing agent. The 2,4,5-triaryloxazoles were prepared analogously from benzoin and aromatic nitriles. Typically, 2-(2-chlorophenyl)-4-(4-diethylaminophenyl)-5-phenyloxazole was prepared by condensing 4-diethylaminobenzoin and 2-chlorobenzonitrile in concentrated sulfuric acid.²¹

Loop and his co-workers^{110,133-136} have extended this reaction not only by using simple and mixed aliphatic-aromatic acyloins but also their

¹³² F. R. Japp and T. S. Murray, *J. Chem. Soc.* **63**, 469 (1893).

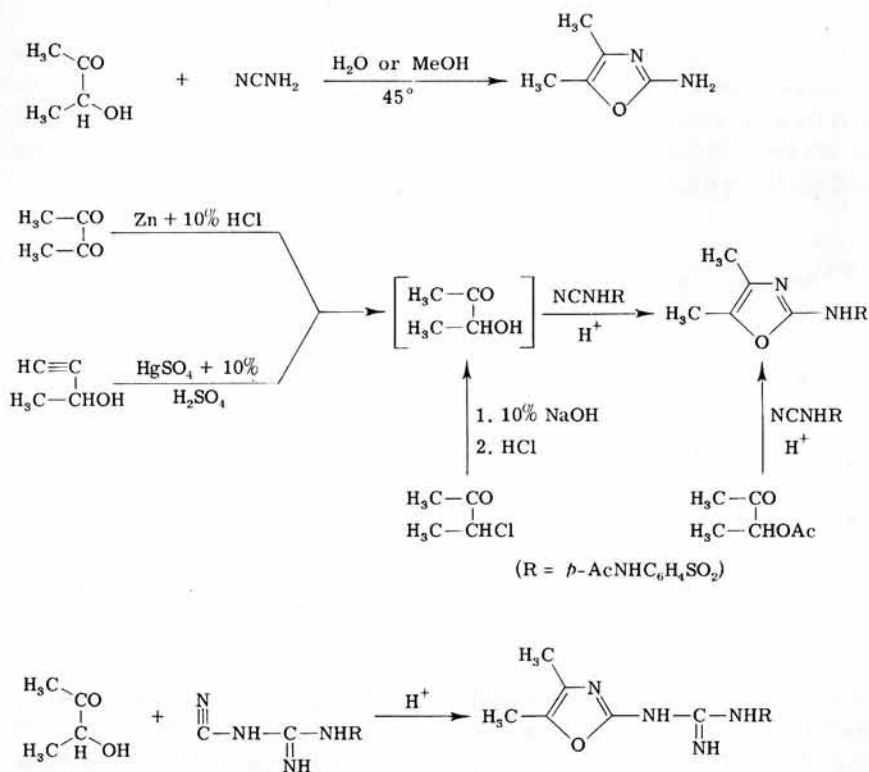
¹³³ V. Wolf and W. Loop, German Patent 1,121,052 (1962); *Chem. Abstr.* **57**, 833 (1962).

¹³⁴ V. Wolf and W. Loop, German Patent 1,128,429 (1962); *Chem. Abstr.* **57**, 13758 (1962).

¹³⁵ W. Loop, H.-J. May, and H. Baganz, *Chem. Ber.* **102**, 230 (1969).

¹³⁶ W. Loop, H. Baganz, F. W. Kohlmann, and H. Schutze, U.S. Patent 3,562,258 (1971); *Chem. Abstr.* **75**, 5878 (1971).

precursors which would produce acyloins as intermediates during the course of the reaction. Furthermore, the nitrile component has been replaced by cyanamide; sodium or calcium cyanamide; *p*-aminobenzene-sulfonyl cyanamide and its acetyl derivative, dicyanamide; *N*³-substituted cyanoguanidines; *N*-cyanoamidine, etc. Some of the typical reactions leading to the formation of *N*-substituted 2-aminooxazoles are illustrated in Scheme 3.



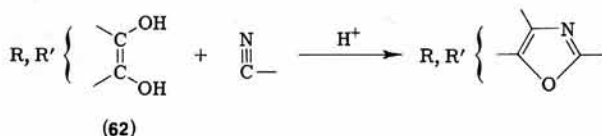
Scheme 3

Oxazoles are also obtained by heating acetylenic alcohols, in which the acetylenic bond is in the α,β -position to the hydroxy group, with acid amides in the presence of a mercury salt catalyst,¹³⁷ or alternatively, by heating α -ketol acetates with nitriles in sulfuric acid.¹³⁸ In those cases

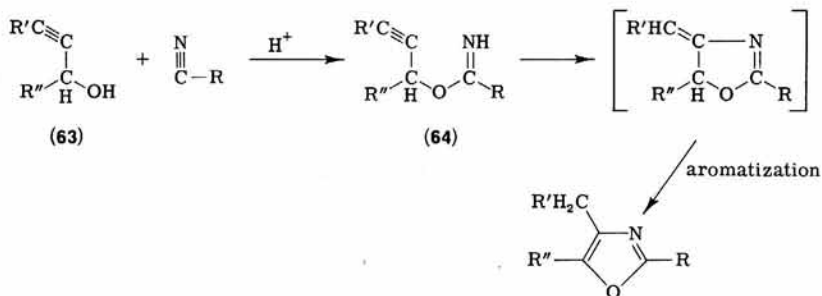
¹³⁷ W. Reppe and A. Magin, French Patent 1,240,996 (1963); *Chem. Abstr.* **60**, 5506 (1964).

¹³⁸ A. Isard, French Demande 2,074,731 (1971); *Chem. Abstr.* **77**, 48443 (1972).

where α -hydroxy ketones with two different substituents (**62**) are involved as intermediates, isomeric 4,5-disubstituted oxazoles may be formed.^{135, 137}



In a related synthesis, acetylenic carbinols (**63**) have been claimed to condense directly with nitriles in the presence of concentrated sulfuric acid to give substituted oxazoles.¹³⁹ Intermediates of the type represented by **64** have in fact been prepared independently as their hydrochlorides and are known to give oxazoles on treatment with sulfuric acid.¹⁴⁰



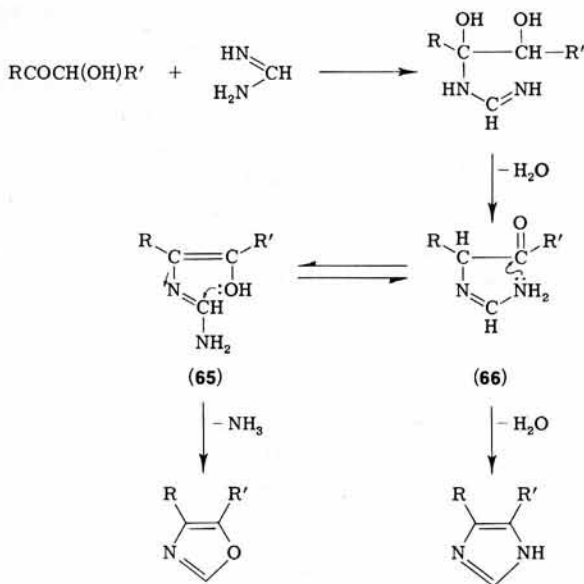
I. FROM α -HYDROXY KETONES AND FORMAMIDINE

Bredereck *et al.*^{10, 95} have pointed out that whereas the reaction of aliphatic acyloins with formamidine affords mainly imidazoles (35–68% yield), the benzoin yields predominantly oxazoles (67–90% yield), irrespective of the alteration in reaction conditions. α -Hydroxybutyrophenone occupies an intermediate position and gives rise to both the oxazole and imidazole derivatives. Unlike formamidine, acetamidine and benzamidine react with both acyloins and benzoin, giving imidazoles exclusively. The reaction is proposed¹⁰ to occur as in Scheme 4.

It has been suggested that aryl groups favor structure **65**, derived from the enediol form of the hydroxy ketones (and hence the formation of oxazoles), whereas the alkyl groups favor **66** and consequently yield imidazoles. The observation that higher amidines give only imidazoles

¹³⁹ Y. Yura, Japanese Patent 29849 (1964); *Chem. Abstr.* **62**, 11818 (1965).

¹⁴⁰ Y. Yura, Japanese Patent 10130 (1964); *Chem. Abstr.* **61**, 12006 (1964).



Scheme 4

is probably due to the steric hindrance to reaction of enolic oxygen with the amidine carbon atom.¹⁰

Another closely related synthesis of oxazoles is the reaction between tris(formylamino)methane and benzoin at 140° . Other keto compounds give either a mixture of oxazoles and imidazoles or only oxazoles.^{10, 95}

J. FROM BENZILS AND AMMONIA

One of the first recognized preparations of an oxazole was that of 2,4,5-triphenyloxazole by the action of ammonia on benzil.¹⁴¹ The reaction is very complex and leads to a variety of products (including 2,4,5-triphenylimidazole) depending on the temperature, time, and solvent. A number of mechanisms to explain the mode of formation of these products have already been critically discussed in previous reviews.^{1, 4} In the latest study by Wenkert and Mekler,¹⁴² the reaction between benzil and ammonia is interpreted as involving the ionic cleavage of a benzil-ammonia complex containing two benzil units.

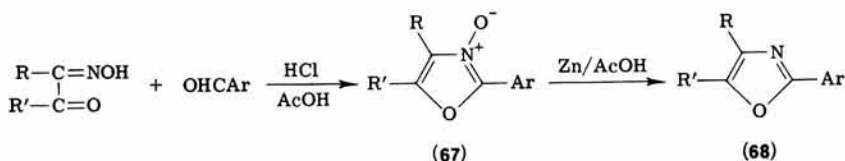
The scope of this synthetic method is too narrow, and therefore is only of theoretical interest.

¹⁴¹ N. Zinin, *Liebigs Ann. Chem.* **34**, 186 (1840).

¹⁴² E. Wenkert and A. B. Mekler, *J. Amer. Chem. Soc.* **78**, 2213 (1956).

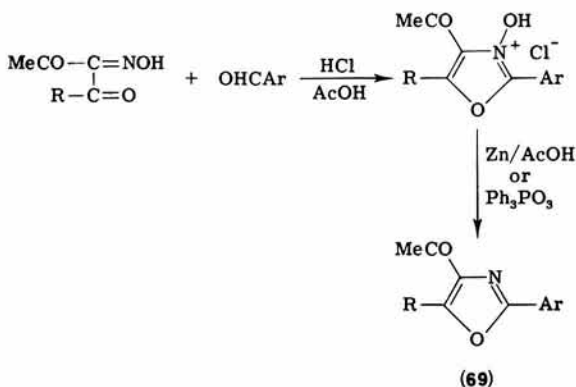
K. FROM α -HYDROXYIMINO KETONES AND ALDEHYDES

The synthesis of oxazoles from α -hydroxyimino ketones was originally described by Diels and Riley,¹⁴³ and the method was later extended by Dilthey and Friedrichsen,¹⁴⁴ and Selwitz and Kosak.¹⁴⁵ The method involved condensation of α -hydroxyimino ketones with aromatic aldehydes in the presence of dry hydrogen chloride to form oxazole *N*-oxides (67) which could easily be reduced with zinc in acetic acid to the free base (68). Catalytic reduction (Ni/H_2) is also effective for the final stage.¹⁴⁶



Alicyclic oximino ketones are found to react similarly. 1,2,3-Cyclohexanetrione-1,3-dioxime has thus been transformed into 2-phenyl-7-hydroxyimino-4,5,6,7-tetrahydrobenzoxazole-3-oxide.¹⁴⁵

Hydroxyimino β -diketones have been shown to react with aromatic



¹⁴³ O. Diels and D. Riley, *Ber.* **48**, 897 (1915).

¹⁴⁴ W. Dilthey and J. Friedrichsen, *J. Prakt. Chem.* **127**, 292 (1930).

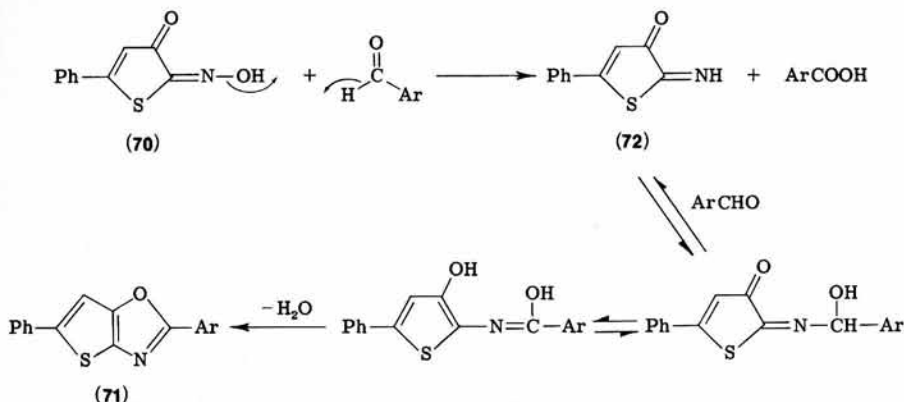
¹⁴⁵ C. M. Selwitz and A. I. Kosak, *J. Amer. Chem. Soc.* **77**, 5370 (1955).

¹⁴⁶ K. Bodendorf and H. Towliati, *Arch. Pharm. (Weinheim)* **298**, 293 (1965).

aldehydes to give, after reduction of the intermediate oxazole *N*-oxide hydrochlorides, the corresponding 4-acetyloxazoles (69).¹⁴⁷

Until recently the reaction was restricted to the synthesis of trisubstituted oxazoles only, using substituted benzaldehydes as the aldehyde component. Weintraub¹⁴⁸ has now extended the reaction by using not only aliphatic aldehydes (including formaldehyde) but also α -ketoal-doximes. Thus 4,5- and 2,5-diaryloxazoles have been prepared by this method. Heterocyclic aldehydes can also be employed with success.

o-Quinone monoximes under similar conditions are usually found to give fused imidazoles, presumably because the monoximes often disproportionate. The only example available in the literature where fused oxazole derivative was obtained by the condensation of an *o*-quinone monoxime with an aldehyde was described by Selwitz and Kosak.¹⁴⁵ 5-Phenyl-2,3-thiophenequinone-2-oxime (70) when refluxed with excess of aromatic aldehydes gave the respective substituted thieno[2,3-*d*]oxazoles (71).

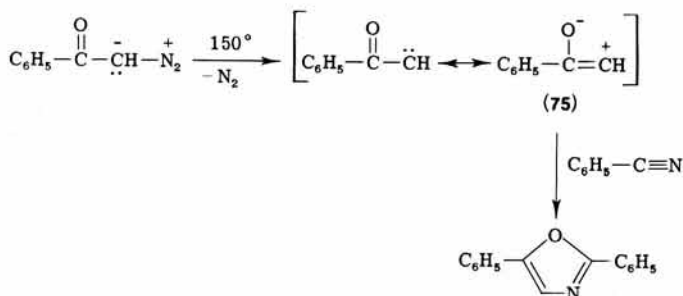


It has formally been represented that the monoxime (70) is first reduced by the action of aldehyde to the corresponding monoimine (72) (a structural type which has been¹⁴⁹ converted into the oxazole nucleus under similar conditions), which then reacts with another molecule of aldehyde to give the oxazole (71).

¹⁴⁷ A. W. Allan and B. H. Walter, *Chem. Ind. (London)*, 1340 (1965); *J. Chem. Soc. C*, 1397 (1968).

¹⁴⁸ P. M. Weintraub, *J. Med. Chem.* **15**, 419 (1972).

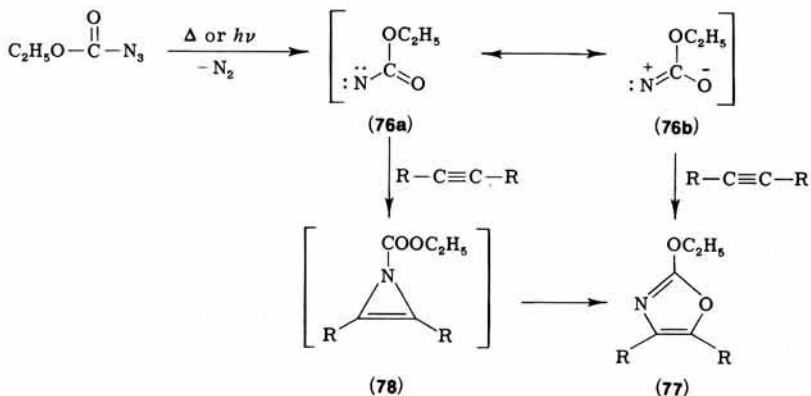
¹⁴⁹ C. W. C. Stein and A. R. Day, *J. Amer. Chem. Soc.* **64**, 2567, 2569 (1942).



In a similar fashion, the thermal decomposition of diazoacetic ester in benzonitrile at 145° gave 2-phenyl-5-ethoxyoxazole (42%).¹⁵⁴

N. FROM ACYL, ARYL, OR α -KETO AZIDES

The thermal or photolytic decomposition of carbonyl azides in the presence of dipole acceptors such as acetylenes provides a valuable method for the construction of oxazoles. Thus the reaction of ethyl azidoformate with either diphenyl- or diethylacetylene produces mainly the 2-ethoxyoxazole (77).^{155, 156} The reaction involves the 1,3-dipolar cycloaddition of carbethoxy nitrene (76b) to the alkyne to give the oxazole (77). On the



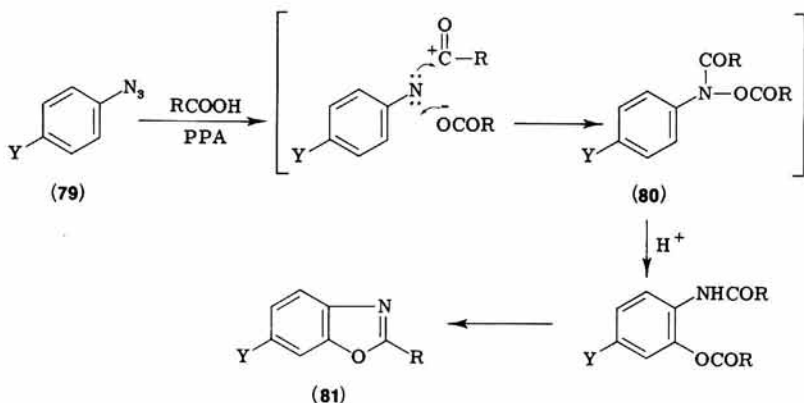
contrary, the addition of nitrene (76a) to the alkyne would appear to give the 2-azirine (78); however, it has not been isolated.¹⁵⁵

¹⁵⁵ R. Huisgen and H. Blaschke, *Tetrahedron Lett.*, 1409 (1964); *Chem. Ber.* **98**, 2985 (1965).

¹⁵⁶ J. Meinwald and D. H. Aue, *J. Amer. Chem. Soc.* **88**, 2849 (1966).

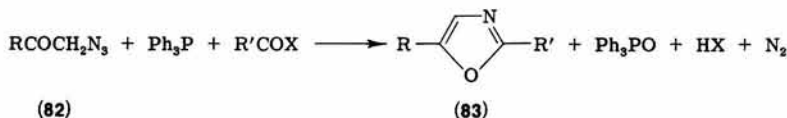
The photodecomposition of acetyl azide in phenylacetylene similarly affords 2-methyl-5-phenyloxazole.¹⁵⁷

A simple, though limited, method of synthesizing benzoxazoles, which does not necessitate the use of ortho-disubstituted starting materials, was discovered by Garner, Mullock, and Suschitzky.¹⁵⁸ They found that aromatic azides (**79**) having an electronegative para substituent decompose thermally in a mixture of a carboxylic acid and polyphosphoric acid to give benzoxazoles (**81**) in good yields. The benzoxazoles (**81**) are believed to result via the intermediate formation of *N,O*-diacyl arylhydroxylamines (**80**) from the initially formed nitrenes, followed by their rearrangement into the acylated *o*-aminophenols and subsequent cyclization.¹⁵⁸ Thus,



p-nitrophenyl and *p*-carboxyphenyl azide on heating in a mixture of acetic and polyphosphoric acids give 6-nitro- and 6-carboxybenzoxazole, respectively, in 83% yields. 3,4-Disubstituted aryl azides give a mixture of two isomeric benzoxazoles.¹⁵⁸

Recently, a novel method of oxazole synthesis involving the simultaneous reaction of an α -azido carbonyl compound (**82**), triphenylphosphine, and an acyl halide has been introduced by Zbiral, Bauer, and Stroh.¹⁵⁹

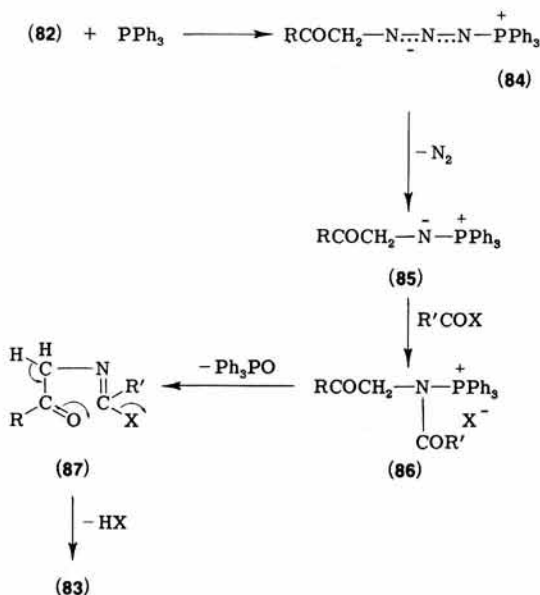


¹⁵⁷ R. Huisgen and J.-P. Anselme, *Chem. Ber.* **98**, 2998 (1965).

¹⁵⁸ R. Garner, E. B. Mullock, and H. Suschitzky, *J. Chem. Soc. C*, 1980 (1966).

¹⁵⁹ E. Zbiral, E. Bauer, and J. Stroh, *Monatsh. Chem.* **102**, 168 (1971).

Thus oxazoles (**83**) substituted in the 2-position by an alkyl, cyclopropyl, or pentadienyl group and in the 5-position by a phenyl, substituted phenyl, or lower alkoxy groups have been obtained in 22–68% yields. The reaction is usually carried out in benzene solution at room temperature or at 70°. The initial step in the reaction is considered to be the formation of the triazene structure (**84**) from the α -azidocarbonyl compound (**82**) and triphenylphosphine, which by the irreversible loss of nitrogen gives the intermediate ylide (**85**). Its *N*-acylation to **86** is accompanied by the elimination of Ph_3PO through a rearrangement to give the imido halogenide (**87**), which readily dehydrohalogenates to yield the oxazole (**83**).¹⁵⁹

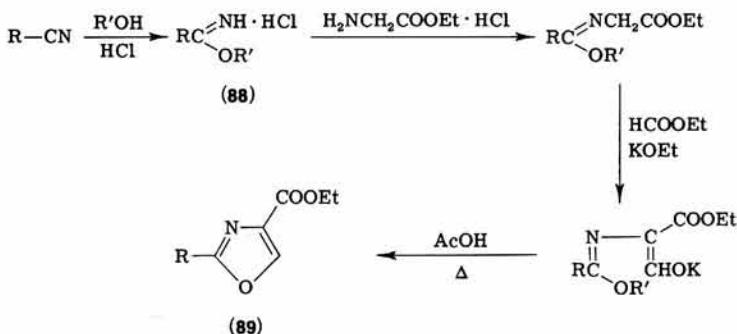


O. FROM IMINO ETHERS

Cornforth *et al.*² have devised a flexible method of synthesizing oxazoles (89) from the condensation of an imino ether (88) and ethyl glycinate hydrochloride, followed by reaction with an alkyl formate and potassium alkoxide, and cyclization of the product in hot acetic acid. The reported yields in various stages are fairly good.

The starting nitrile may be alkyl, aryl, or even hydrogen cyanide, which leads to the synthesis of oxazole itself¹⁶⁰ by hydrolysis and decarboxylation of the oxazole-4-carboxylate (**89**, R = H). Various exten-

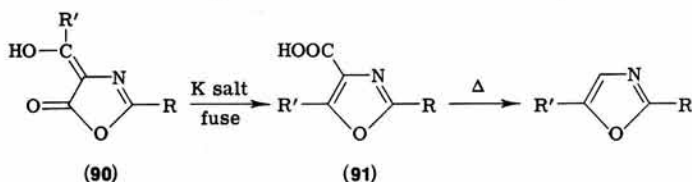
¹⁶⁰ J. W. Cornforth and R. H. Cornforth, *J. Chem. Soc.*, 96 (1947).



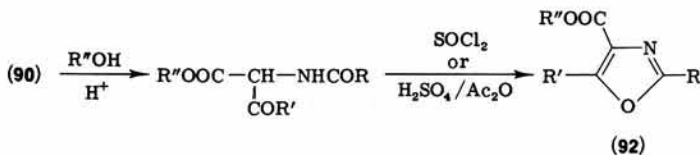
sions of this synthesis are possible. Replacement of glycine ester with aminoacetonitrile affords 4-cyanooxazoles,^{161,162} while that of formic ester with oxalic ester gives oxazole-4,5-dicarboxylates.¹²⁹

P. FROM 5-OXAZOLONES

Fusion of the sodium or potassium salt of 4-(α -hydroxyalkylidene)-2-oxazoline-5-ones (**90**) leads, by rearrangement, to oxazole-4-carboxylic acids (**91**) which can easily be decarboxylated to the corresponding oxazoles.^{2,4} This rearrangement occurs also in alkali, and a ¹⁴C tracer



study has substantiated a mechanism involving ring-opening followed by the alternative ring closure.¹⁶³ The heterocyclic ring in **90** is cleaved by alcoholic hydrogen chloride to form alkyl α -acylaminoacylacetates, which are cyclized to give oxazole-4-carboxylates (**92**).³⁸

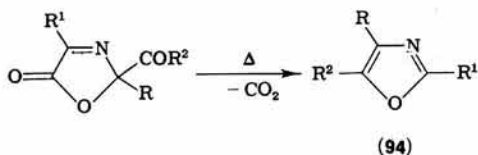
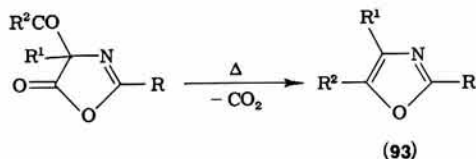


¹⁶¹ T. P. Sycheva, T. Kh. Trupp, and M. N. Shchukina, *Zh. Obshch. Khim.* **32**, 1071 (1962); *J. Gen. Chem. USSR* **32**, 1051 (1962).

¹⁶² T. P. Sycheva, T. N. Pavlova, and M. N. Shchukina, *Khim. Geterotsikl. Soedin.*, **7** (1972); *Chem. Abstr.* **76**, 153652 (1972).

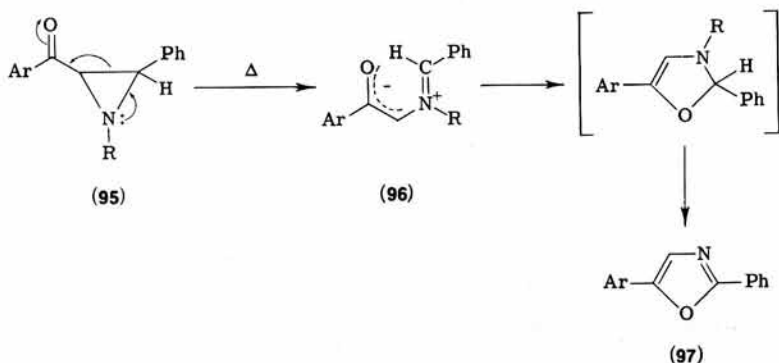
¹⁶³ C. G. Stuckwisch and D. D. Powers, *J. Org. Chem.* **25**, 1819 (1960).

Hoefle and Steglich¹⁶⁴ have recently found that thermolysis of 2,4-disubstituted 4-acyl-2-oxazoline-5-ones and 2,4-disubstituted 2-acyl-3-oxazolin-5-ones gives 2,4,5-trisubstituted oxazoles (**93** and **94**, respectively), with elimination of carbon dioxide. In the latter case, the substituents at C-2 and C-4 were interchanged.



Q. FROM OTHER HETEROCYCLES

Numerous thermochemical and photochemical transformations are known to produce oxazoles, although the vast majority of them are not of any synthetic importance. Pyrolysis of a number of *N*-substituted 2-phenyl-3-aryloxaziridines (**95**) gives the corresponding 2-phenyl-5-aryloxazole (**97**), with loss of the nitrogen substituent.¹⁶⁵ The formation of the oxazole

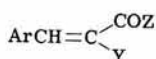


¹⁶⁴ G. Hoefle and W. Steglich, *Chem. Ber.* **104**, 1408 (1971).

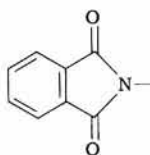
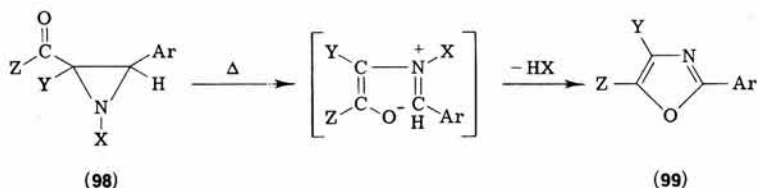
¹⁶⁵ A. Padwa and W. Eisenhardt, *Chem. Commun.*, 380 (1968).

apparently proceeds through carbon-carbon bond scission to give stabilized 1,3-dipole intermediate (96). Subsequent ring closure to a transient 2,3-dihydrooxazole followed by thermal elimination readily accounts for the observed product (97).

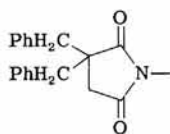
Foucaud and Baudru¹⁶⁶ have reported the preparation of several 5-amino- and 5-alkoxyoxazoles by the thermolysis of *N*-imidoaziridines (98). The latter are readily obtained by the oxidation of *N*-aminophthalimides (A—NH₂) and *N*-aminosuccinimides (M—NH₂ and Q—NH₂) with lead tetracetate in the presence of the *gem*-disubstituted olefins with two electron-attracting groups (with at least one of them of the type —COZ), e.g.,



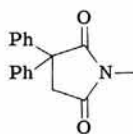
The *N*-imidoaziridines are relatively unstable substances and isomerize, either spontaneously at room temperature or on boiling in an organic solvent, to give the corresponding oxazoles (99).



A



M



Q

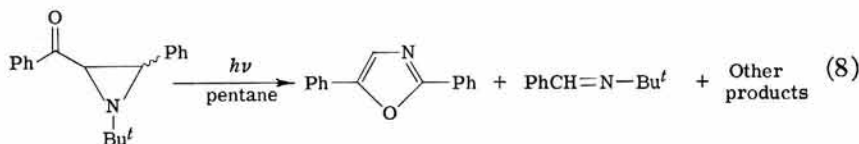
X = A, M, or Q
Ar = C₆H₅ or *p*-ClC₆H₄

Ultraviolet irradiation in pentane of *cis*- and *trans*-*N*-*tert*-butyl-2-phenyl-3-benzoylaziridine (95, Ar = Ph, R = *t*-Bu) affords 2,5-diphenyloxazole in 51% and 38% yields, respectively, besides several other products, as shown in Eq. (8).¹⁶⁷ The course of the overall photo-

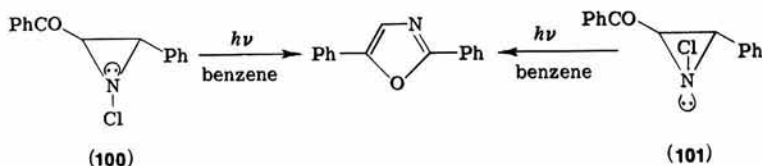
¹⁶⁶ A. Foucaud and M. Baudru, *C. R. Acad. Sci., Ser. C* **271**, 1613 (1970).

¹⁶⁷ A. Padwa and W. Eisenhardt, *J. Amer. Chem. Soc.* **90**, 2442 (1968); **93**, 1400 (1971).

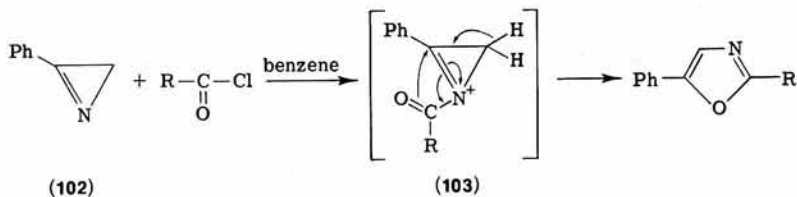
reaction is substantially altered in the two cases. The formation of diphenyloxazole by the photolysis of *trans*-aziridine has been rationalized as in the above thermolytic reaction ($95 \rightarrow 97$).



Further, Padwa and Battisti¹⁶⁸ reported that 2,5-diphenyloxazole is also obtained in high yield (80%) by the irradiation of the invertomers (**100** and **101**) of *N*-chloro-*trans*-2-benzoyl-3-phenylaziridine (prepared by the treatment of *trans*-2-benzoyl-3-phenylaziridine with *tert*-butyl hypochlorite).¹⁶⁸



Japanese workers¹⁶⁹ have found that 2-phenyl-1-azirine (**102**) reacts with acid chlorides and acyclic acid anhydrides in the presence of triethylamine to give, in moderate yields, the corresponding 2-substituted 5-phenyloxazoles. The formation of oxazoles by the reaction of 2-phenylazirine and acid chlorides has been suggested to proceed through the initial formation of intermediate **103**, involving the attack of an acylation on the nitrogen atom of azirine, followed by ring enlargement by cleavage of the C—N linkage.



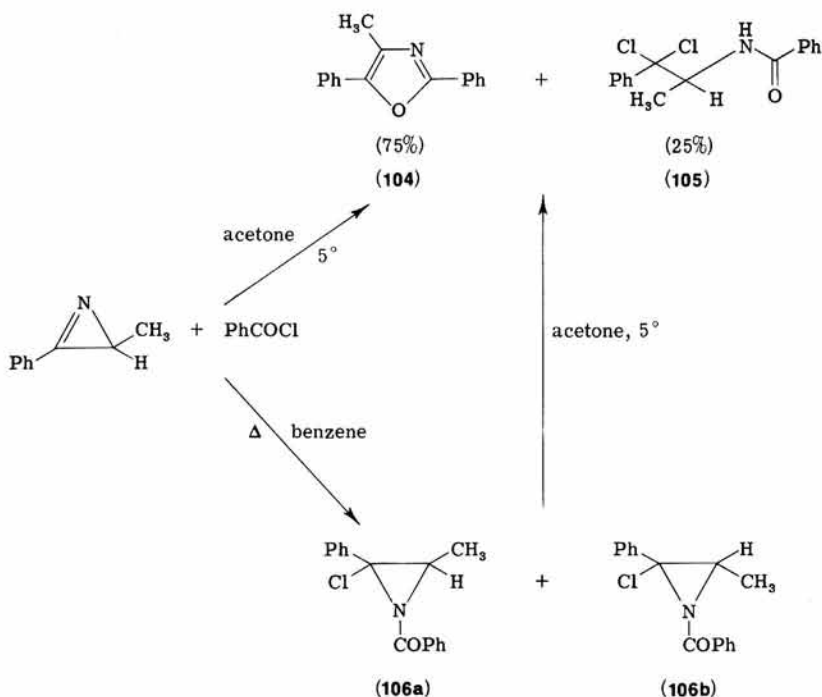
Intermediates of type **103** are in fact known to be involved in the reaction of 3-methyl-2-phenyl-1-azirine with benzoyl chloride.¹⁷⁰ In acetone at

¹⁶⁸ A. Padwa and A. Battisti, *J. Org. Chem.* **36**, 230 (1971).

¹⁶⁹ S. Sato, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jap.* **40**, 1014, 2938 (1967).

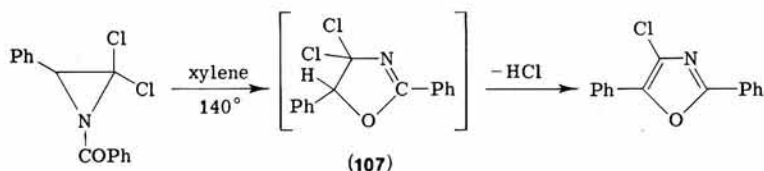
¹⁷⁰ F. W. Fowler and A. Hassner, *J. Amer. Chem. Soc.* **90**, 2875 (1968).

5° they give a mixture of ring-expanded oxazole (**104**) and ring-opened dichloro amide (**105**). The reaction in refluxing benzene, however, makes it possible to isolate the intermediate *N*-benzoyl-2-chloroaziridines (**106a**



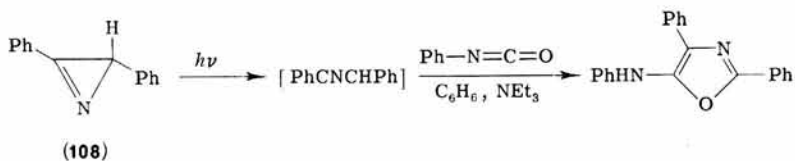
and **106b**). These aziridines are unstable and are readily solvolyzed in polar solvents giving the oxazole (**104**) and a smaller amount of dichloro-amide (**105**). 2,3-Diphenyl-1-azirine behaves similarly and affords triphenyloxazole on reaction with benzoyl chloride.¹⁷⁰

A somewhat related rearrangement was described by Zaugg and DeNet.¹⁷¹ 1-Benzoyl-2,2-dichloro-3-phenylaziridine rearranges thermally to give 4-chloro-2,5-diphenyloxazole in 81% yield. The exact mechanism of the reaction is not known but is believed to proceed through the intermediate **107**.¹⁷¹

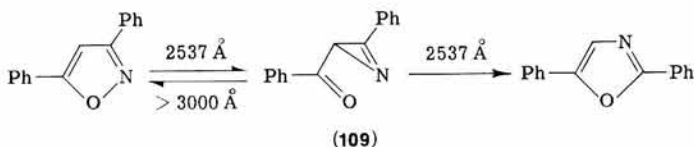


¹⁷¹ H. E. Zaugg and R. W. DeNet, *J. Org. Chem.* **36**, 1937 (1971).

Swiss chemists¹⁷² have recently shown that the photochemical cycloaddition of 2,3-diphenyl-1-azirine (**108**) to phenyl isocyanate in benzene solution gives 2,4-diphenyl-5-phenylaminooxazole in 45% yield.



Several interesting and obviously related rearrangements have been reported for isoxazoles, which by the photochemical transposition of ring atoms change to the corresponding oxazoles. Ullman and Singh,^{173,174} while studying the photorearrangement of 3,5-diphenylisoxazole to 2,5-diphenyloxazole, observed the formation of 2-phenyl-3-benzoyl-1-azirine (**109**) as a true intermediate and noted that the azirine (**109**) was dramatically sensitive to different wavelengths of light. Irradiation of **109** in ether at 2537 Å resulted in an up to 84% conversion to 2,5-diphenyloxazole, whereas irradiation with wavelengths greater than 3000 Å reverted it to the isoxazole. An exactly similar trend was observed in the photochemical rearrangement of 3-*p*-anisyl-5-phenylisoxazole to 2-*p*-anisyl-5-phenyloxazole through 2-*p*-anisyl-3-benzoyl-1-azirine as the intermediate.¹⁷⁴



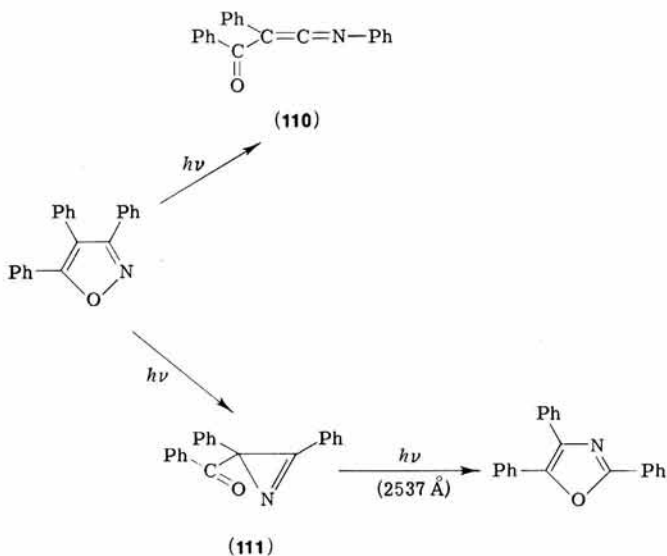
Kurtz and Shechter¹⁷⁵ have found that the irradiation of 3,4,5-triphenylisoxazole in ether or benzene gives *N*-phenyl-benzoylphenylketenimine (**110**, 40%), 3-benzoyl-2,3-diphenyl-1-azirine (**111**), and 2,4,5-triphenyloxazole (~40%).

¹⁷² B. Jackson, N. Gakis, M. Märky, H. J. Hansen, W. v. Philipsborn, and H. Schmid, *Helv. Chim. Acta* **55**, 916 (1972).

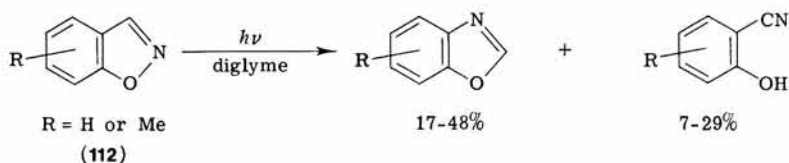
¹⁷³ E. F. Ullman and B. Singh, *J. Amer. Chem. Soc.* **88**, 1844 (1966).

¹⁷⁴ B. Singh and E. F. Ullman, *J. Amer. Chem. Soc.* **89**, 6911 (1967).

¹⁷⁵ D. W. Kurtz and H. Shechter, *Chem. Commun.*, 689 (1966).



The photoisomerizations of this type appear to be quite general, but the yield of the oxazoles varies considerably. Thus ultraviolet irradiation of 3,5-dimethylisoxazole in methanol gives an 80% yield of 2,5-dimethyloxazole.¹⁷⁶ 1,2-Benzisoxazoles (112) similarly rearrange to benzoxazoles together with some substituted *o*-hydroxybenzonitriles as by-products.¹⁷⁶



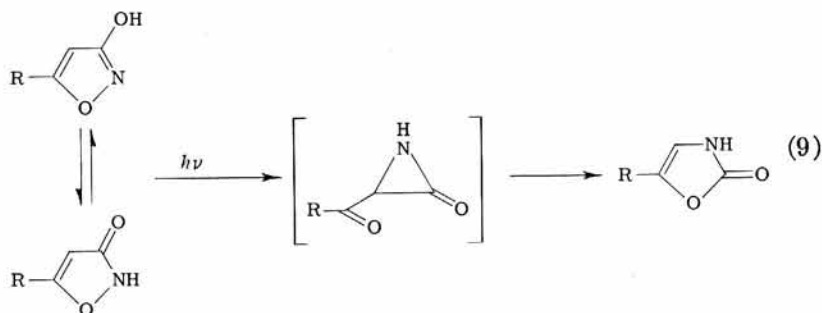
Goeth *et al.*¹⁷⁷ prepared a number of 2(3*H*)-oxazolones by the photolysis of the corresponding 3-hydroxyisoxazoles and proposed the rearrangement, as shown in Eq. (9), to occur through azirine derivatives as intermediates.

Jones and Good¹⁷⁸ observed that the photochemical conversion of 3-isoxazolecarboxylates into 2-oxazolecarboxylates could be achieved in

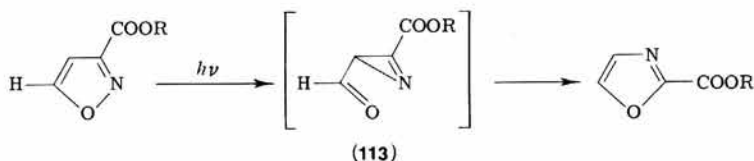
¹⁷⁶ H. Goeth and H. Schmid, *Chimia* **20**, 148 (1966); *Chem. Abstr.* **65**, 3854 (1966).

¹⁷⁷ H. Goeth, A. R. Gagneux, C. H. Eugster and H. Schmid, *Helv. Chim. Acta* **50**, 137 (1967).

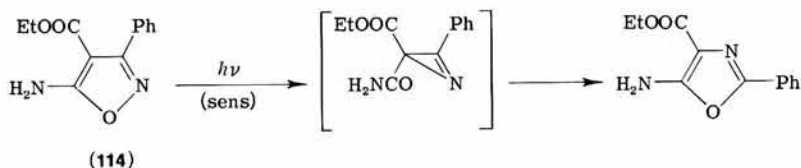
¹⁷⁸ G. Jones and R. H. Good, *J. Chem. Soc. C*, 1196 (1971).



only 5–8% yields. The poor yield of the oxazole is probably due to instability of the intermediate azirine aldehyde (**113**).



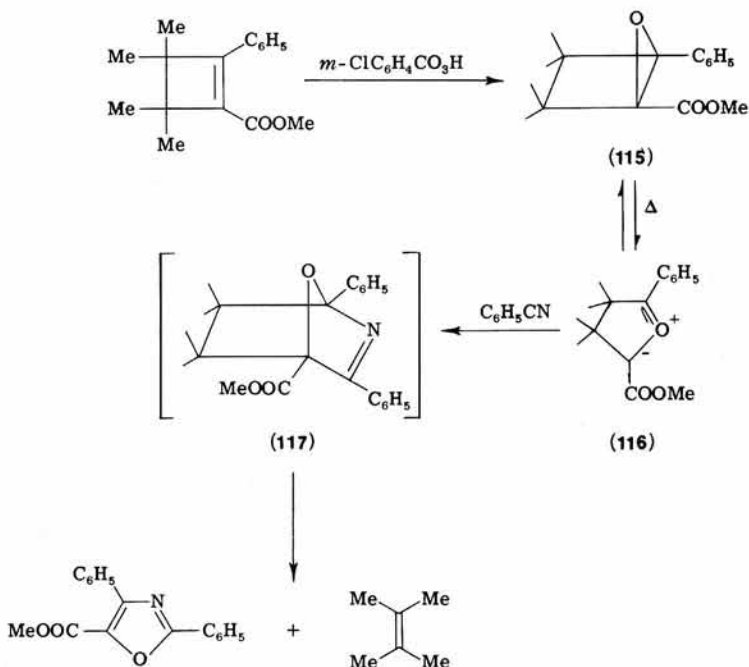
5-Amino-4-ethoxycarbonyl-3-phenylisoxazole (**114**) similarly photoisomerizes in the presence of triphenylene to give 5-amino-4-ethoxycarbonyl-2-phenyloxazole.¹⁷⁹



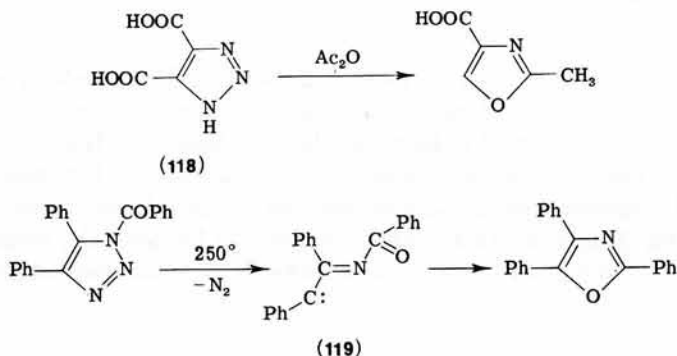
An interesting synthesis of methyl 2,4-diphenyloxazole-5-carboxylate has been reported by Arnold and Chang.¹⁸⁰ When 1-carbomethoxy-4-phenyl-2,2,3,3-tetramethyl-5-oxabicyclo[2.1.0]pentane (**115**) was heated to 120° in the presence of benzonitrile, a good yield of the oxazole was obtained, together with tetramethylethylene. The colored carbonyl ylide (**116**), formed upon heating, adds a molecule of benzonitrile, presumably to form the adduct **117** which via a retro-Diels-Alder reaction gives the products.

¹⁷⁹ H. Wamhoff, *Chem. Ber.* **105**, 748 (1972).

¹⁸⁰ D. R. Arnold and Y. C. Chang, *J. Heterocycl. Chem.* **8**, 1097 (1971).



Treatment of 1,2,3-triazole-4,5-dicarboxylic acid (118) with acetic anhydride leads to 2-methyloxazole-4-carboxylic acid.¹⁸¹ The mechanism of the reaction is not yet clear, but it may be related to the thermal decomposition of 1-benzoyl-4,5-diphenyl-1,2,3-triazole, which on heating above 250° gives 2,4,5-triphenyloxazole (29%), presumably through the acyliminocarbene intermediate 119.¹⁸²

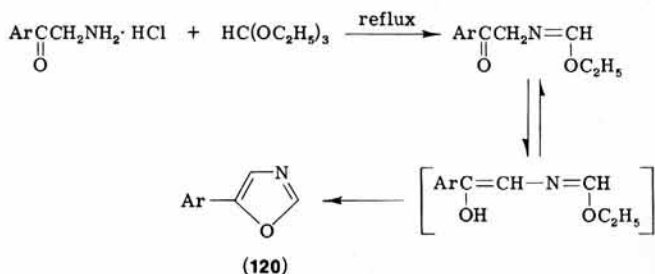


¹⁸¹ D. J. Anderson, T. L. Gilchrist, and C. W. Rees, *Chem. Commun.*, 147 (1969).

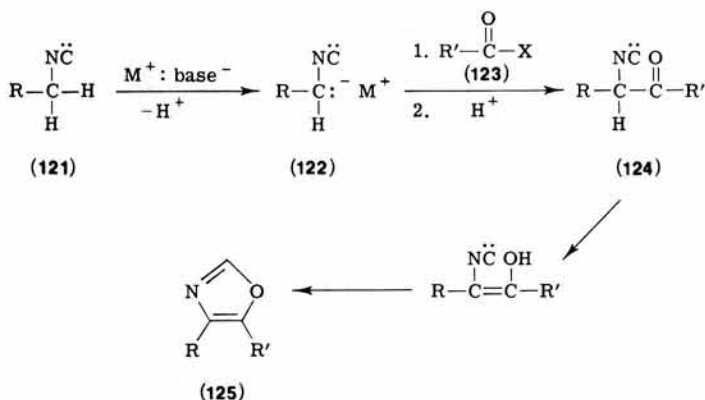
¹⁸² R. Huisgen, *Angew. Chem.* **72**, 359 (1960).

R. MISCELLANEOUS METHODS

Demchenko and Grekov¹⁸³ found that 5-monoaryl oxazoles (120) could readily be obtained by heating the hydrochlorides of aminomethyl aryl ketones with an excess of ethyl orthoformate.



2-Unsubstituted oxazoles (125) can be obtained conveniently by treating α -metalated alkyl isocyanides (122) [prepared from isocyanides (121) and, for example, potassium *tert*-butoxide or butyl lithium] with acylating agents (123). Intermediates in this synthesis are presumably the 2-oxoalkyl isocyanides (124) which, *in situ* or during the working up, cyclize by way of their enolic forms. Acylating agents employed included acyl chlorides, carboxylic esters, and N,N-disubstituted amides; they lead to 4,5-di- or 5-monosubstituted oxazoles in fairly good yields in a single operation.¹⁸⁴



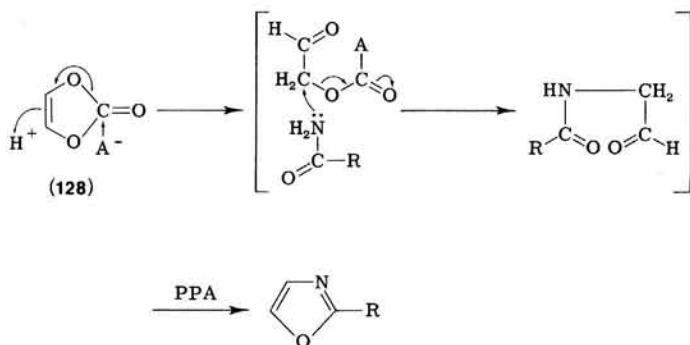
Treatment of β -aminocrotonic esters, or the enamines of β -diketones,

¹⁸³ N. P. Demchenko and A. P. Grekov, *Zh. Obshch. Khim.* **32**, 1219 (1962); *J. Gen. Chem. USSR* **32**, 1192 (1962).

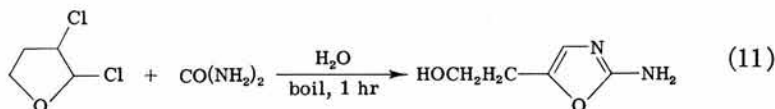
¹⁸⁴ U. Schöllkopf and R. Schröder, *Angew Chem. Int. Ed. Engl.* **10**, 333 (1971).

¹⁸⁶ P. G. Ferrini and A. Marxer, *Angew. Chem.* **75**, 165 (1963); *Angew. Chem. Int. Ed. Engl.* **2**, 99 (1963).

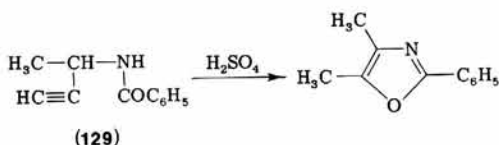
in poor yields. The formation of the oxazole derivatives has been proposed to occur through the intermediate acylaminoacetaldehyde which is cyclized by PPA.



Boiling 2,3-dichlorotetrahydrofuran^{187,188} with urea in water gives a low yield of 2-aminooxazole-5-ethanol [Eq. (11)].



The cyclization of 3-benzamido-1-butyne (129) in cold sulfuric acid gives 2-phenyl-4,5-dimethyloxazole.¹⁸⁹



Huisgen and his co-workers¹⁹⁰ have recently reported that the addition of aromatic nitrile ylides to carbonyl compounds results in the formation of Δ^3 -oxazolines, which are easily oxidizable to oxazoles. Typically, benzonitrile 4-nitrobenzylide (131, Ar = *p*-O₂NC₆H₄), generated from the imidoyl chloride (130) by 1,3-elimination of hydrogen chloride with triethylamine, reacts smoothly with benzaldehyde to give a pair of

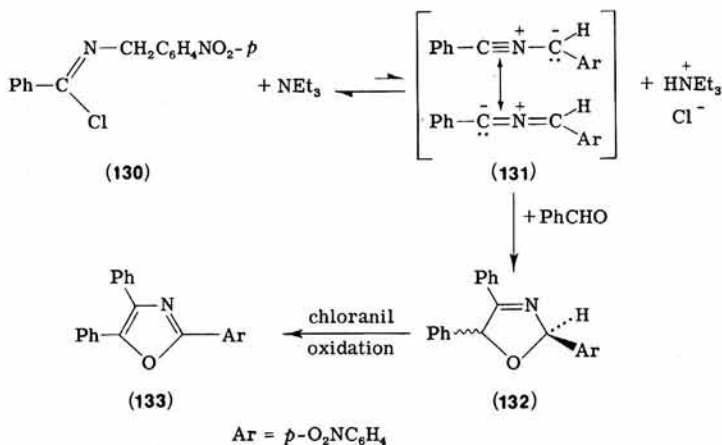
¹⁸⁷ W. Reppe, *Liebigs Ann. Chem.* **596**, 80 (1955).

¹⁸⁸ F. Ebel, H. Pasedach, and M. Seefelder, German Patent 936,986 (1955); *Chem. Abstr.* **52**, 20197 (1958).

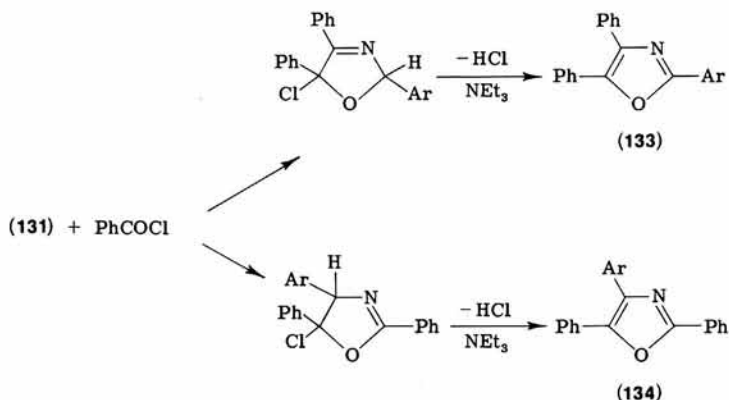
¹⁸⁹ Y. Yura, Japanese Patent 10,129 (1964); *Chem. Abstr.* **61**, 12006 (1964).

¹⁹⁰ K. Bunge, R. Huisgen, R. Raab, and H. Stangl, *Chem. Ber.* **105**, 1279 (1972).

stereoisomers of 4,5-diphenyl-2-*p*-nitrophenyl-3-oxazoline (132), which on oxidation with chloranil yield the corresponding oxazole (133).



The formation of two isomeric oxazole derivatives (133 and 134) from the nitrile ylide (131) and benzoyl chloride is explained by cycloaddition via chlorodihydrooxazoles or by 1,5-dipolar cyclization of benzoylated nitrile ylides.



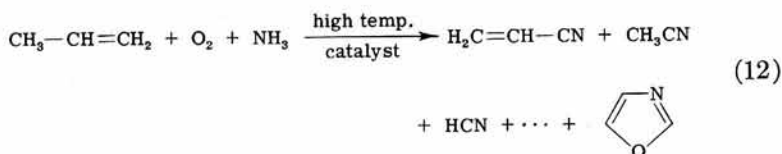
Several patents¹⁹¹⁻¹⁹³ refer to the formation of very small amounts of

¹⁹¹ C. J. Brown, British Patent 1,130,846 (1968); *Chem. Abstr.* **70**, 28909 (1969).

¹⁹² R. Alliot, R. Jobert, and C. Darcas, German Offen. 1,957,926 (1970); *Chem. Abstr.* **73**, 66070 (1970).

¹⁹³ Uguine Kuhlmann, British Patent 1,223,790 (1971); *Chem. Abstr.* **74**, 126387 (1971).

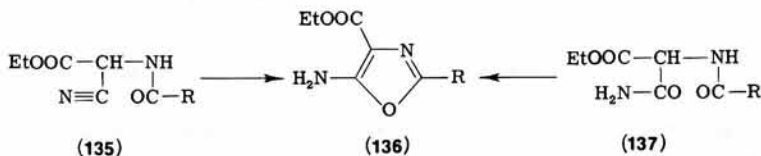
oxazole as a by-product in the manufacture of acrylonitrile. Treating propylene at elevated temperatures in the vapor phase with air and ammonia over an oxidation catalyst gives acrylonitrile (76%) and 0.02% oxazole [Eq. (12)].¹⁹¹ Recovery of oxazole may be achieved by passage



of the mixture through a column of activated adsorbent¹⁹¹⁻¹⁹³ such as Clarsil PC-1 or alumina, or through a cation-exchange resin.¹⁹⁴ Oxazole may also be separated by precipitation as metal complexes^{195,196} with metal salts such as HgCl_2 , CdCl_2 , CdBr_2 , CuCl_2 , ZnCl_2 , CoCl_2 , NiCl_2 , or $\text{Zn}(\text{NO}_3)_2$ which are decomposed by distillation from aqueous suspensions.

S. 5-AMINOXAZOLES

During work on the chemistry of penicillin a variety of methods were developed for the synthesis of 5-aminooxazoles. It has been found that cycloisomerization of acylaminocyanoacetic esters (**135**) by treatment with hydrogen chloride (in alcohol, ether or acetone), phosphorus pentoxide, or pentachloride leads to 5-aminooxazole-4-carboxylic esters (**136**),^{2,61} which have also been obtained by dehydration of acylaminomalonic esters (**137**) with phosphorus oxychloride.²



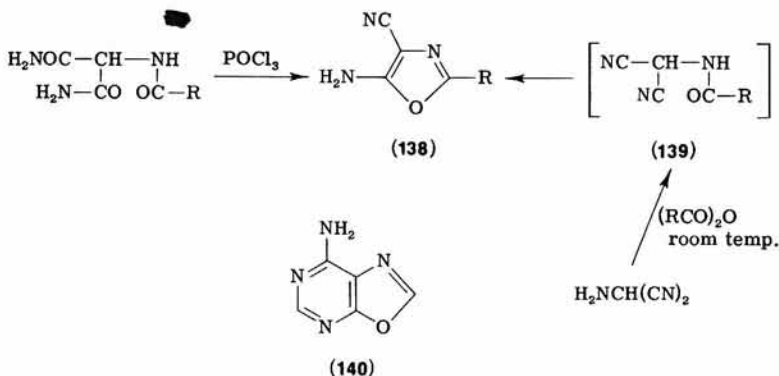
On the other hand, α -acylaminomalondiamides and phosphorus oxychloride afford 5-amino-4-cyanooxazoles (**138**),² which can also be prepared directly by the reaction of aminomalnonitrile with acid anhydrides at

¹⁹⁴ C. Darcas and C. Tcherkowsky, U.S. Patent 3,574,687 (1971); *Chem. Abstr.* **75**, 35997 (1971).

¹⁹⁵ R. H. Hall and D. F. Francis, French Patent 1,539,255 (1968); *Chem. Abstr.* **71**, 124406 (1969).

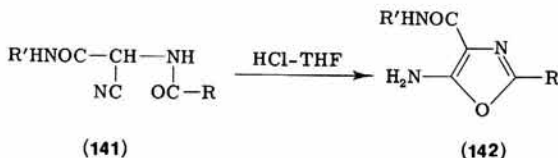
¹⁹⁶ R. L. Maute, U.S. Patent 3,686,263 (1972); *Chem. Abstr.* **77**, 140727 (1972).

room temperature.^{197, 198} The latter reaction most probably occurs through acylaminomalononitriles (139). Treatment of aminomalononitrile with



a mixture of acetic anhydride and formic acid results in the formation of 4-cyano-5-aminooxazole (138, R = H) which condenses with formamidine acetate to give 7-aminooxazolo[5,4-*d*]pyrimidine (140), an adenine analog.¹⁹⁸

Cyclization of 2-acylamino-2-cyanoacetamides (141) under the influence of hydrogen chloride in tetrahydrofuran gives 5-aminooxazole-4-carboxamides (142, R and R' = H and/or Me).¹⁹⁹ Heating 141 with acetic anhydride in the presence of perchloric acid or with a mixture of



formic acid and acetic anhydride in the presence of hydrochloric acid leads to 5-acetamido- and/or 5-formamidooxazole-4-carboxamides.²⁰⁰

A number of 2-aryl-5-aminooxazoles (144) with methyl or phenyl substituents at position 4 have been synthesized by Fleury *et al.*^{201, 202} by the acid-catalyzed cyclization of α -aroylaminoacetonitriles (143) in

¹⁹⁷ J. P. Ferris and L. E. Orgel, *J. Amer. Chem. Soc.* **87**, 4976 (1965).

¹⁹⁸ J. P. Ferris and L. E. Orgel, *J. Amer. Chem. Soc.* **88**, 3829 (1966).

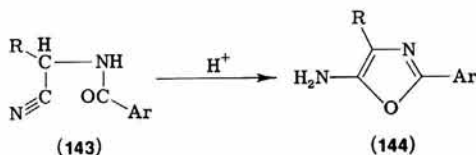
¹⁹⁹ M. Sekiya and J. Suzuki, *Chem. Pharm. Bull.* **18**, 2242 (1970).

²⁰⁰ M. Sekiya, J. Suzuki, and Y. Kakiya, *Chem. Pharm. Bull.* **18**, 1233 (1970).

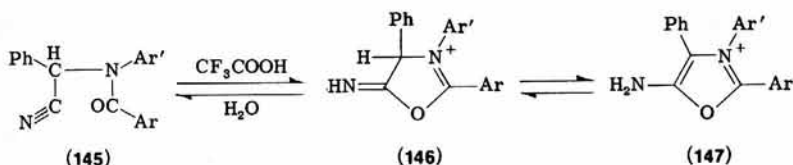
²⁰¹ G. Kille and J.-P. Fleury, *Bull. Soc. Chim. Fr.*, 4619 (1967).

²⁰² J.-P. Fleury, A. Baysang, and D. Clerin, *Bull. Soc. Chim. Fr.*, 4108 (1969).

the presence of hydrochloric, trifluoroacetic, or chlorosulfonic acid. When the substituent at position 4 in **144** is hydrogen, only oxazoles are isolated,



as their salts or 5-trifluoroacetamido derivatives.²⁰³ N-Substituted α -acylaminonitriles (**145**) are cyclized similarly in the presence of strong acids to form the corresponding 5-iminooxazoline salts (**146**) or 5-amino-oxazole salts (**147**), depending on the nature of the substituents.²⁰⁴



Condensation of α -phenyl- α -acylaminoacetonitriles with aromatic or aliphatic aldehydes by heating at 140° in the presence of zinc chloride, or by treatment in alcohol or chloroform with dry hydrogen chloride, produces Schiff bases of 2-aryl (or alkyl)-4-phenyl-5-aminoxazoles.²⁰⁵ The reaction of benzaldehyde with benzene sulfonamide and potassium cyanide (molar ratio 1.0:0.33:~0.2-0.25) at 135° gives a 9-22% yield of 2,4-diphenyl-5-(benzylideneamino)oxazole and has been proposed to proceed through α -benzoylamino phenylacetonitrile.²⁰⁶

Hirobe, Sato, and Okamoto²⁰⁷ have found that iminonitriles (**148**) react with an appropriate aromatic aldehyde in chloroform to form 2,4-diaryl-5-aminoxazoles (**149**) and/or the corresponding 5-arylidene derivatives in good yields.

Another synthesis leading to the formation of derivatives of 5-amino-oxazoles has been described by Ketcham and his co-workers.^{208, 209} Con-

²⁰³ J.-P. Fleury and A. Baysang, *Bull. Soc. Chim. Fr.*, 4102 (1969).

²⁰⁴ P. Roesler and J.-P. Fleury, *Bull. Soc. Chim. Fr.*, 4624 (1967).

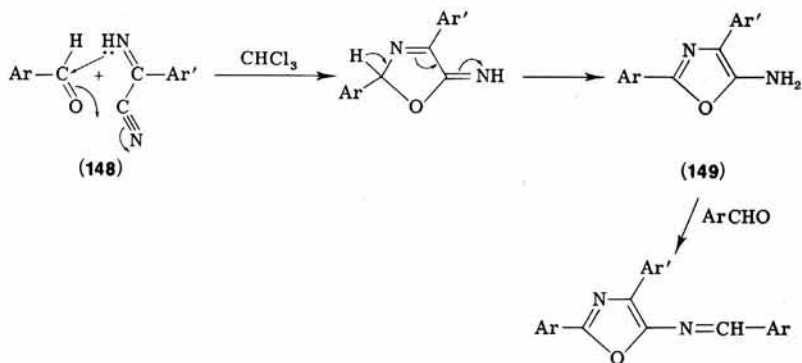
²⁰⁵ J. Lichtenberger and J.-P. Fleury, *Bull. Soc. Chim. Fr.*, 1184 (1956).

²⁰⁶ J. Lichtenberger and J.-P. Fleury, *Bull. Soc. Chim. Fr.*, 1320 (1955).

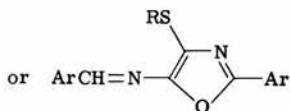
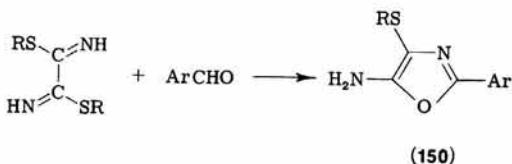
²⁰⁷ M. Hirobe, R. Sato, and T. Okamoto, *Yakugaku Zasshi* **91**, 834 (1971).

²⁰⁸ A. R. Martin and R. Ketcham, *J. Org. Chem.* **31**, 3612 (1966); A. R. Martin, *Diss. Abstr.* **26**, 5734 (1966).

²⁰⁹ R. Ketcham, V. P. Shah, and G. Lam, *J. Med. Chem.* **14**, 456 (1971).



condensation of *S,S'*-dialkyl or *S,S'*-diaryl dithiooxaldiimides with aromatic aldehydes yields 5-amino-4-alkyl (or aryl) mercapto-2-aryloxazoles (150) or the corresponding Schiff bases.²⁰⁸⁻²¹⁰ The Schiff base 5-benzylideneamino-



4-benzylmercapto-2-phenyloxazole, for example, has been reduced with sodium borohydride to the corresponding 5-benzylaminooxazole.²¹⁰

III. Physicochemical Properties

A. CRYSTAL STRUCTURE

No crystal structure has been reported for oxazole itself, which is a liquid at ordinary temperatures, and the simple solid derivatives of oxazole have failed to draw sufficient attention for crystallographic studies.

²¹⁰ S. C. Mutha, Ph.D. Thesis, University of California, San Francisco (1968); *Diss. Abstr. B* 31, 138 (1970).

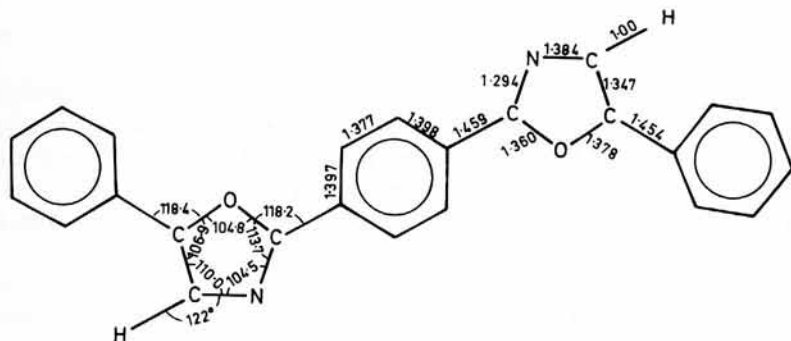


FIG. 1. The geometry of POPOP. [Reproduced with permission from I. Ambats and R. E. Marsh, *Acta Cryst.* **19**, 942 (1965).]

Scatturin *et al.*²¹¹⁻²¹⁴ however, have carried out an investigation of the crystal structure of a number of 2,4-disubstituted 5-*p*-nitrophenyloxazoles. 2-Methyl-4-chloromethyl-5-*p*-nitrophenyloxazole^{211,212} has space group $C_{2h}^5 = P2_1/c$ and a quasi-planar configuration; the angle between the phenyl and oxazole ring is 11° , but the chlorine atom protrudes from the mean molecular plane. Notwithstanding this, 2-methyl-4-bromomethyl-5-*p*-nitrophenyloxazole²¹³ belongs to the space group $Fddd$. X-ray investigation²¹³ of 2,4-dimethyl-5-*p*-nitrophenyloxazole (space group $P2_1$) and 2-chloromethyl-4-methyl-5-*p*-nitrophenyloxazole (space group $P2_1/m$) reveals identical molecular packing for both compounds along the *c* axis and this is attributed to van der Waals interaction.²¹⁴

Recently the crystal structure of the organic scintillator POPOP [2,2'-*p*-phenylenebis(5-phenyl)oxazole] has been determined by x-ray diffraction.²¹⁵ The crystals are monoclinic, space group $P2_1/c$. The three benzene and two oxazole rings are each planar, but they are twisted slightly with respect to one another to form a propeller-shaped molecule. The dihedral angle between the planes of the center phenyl and the oxazole ring is 3.75° and that between the oxazole ring and terminal phenyl group is 6.45° . The bond distances (Fig. 1) indicate appreciable conjugation between the rings and localization of charges within the oxazole rings.²¹⁵

²¹¹ V. Scatturin and R. Zannetti, *Ric. Sci.* **26**, 523 (1956); *Chem. Abstr.* **50**, 16256 (1956).

²¹² V. Albano, P. L. Bellon, F. Pompa, and V. Scatturin, *Ric. Sci., Parte 2: Sez. A* **3**, 1143 (1963); *Chem. Abstr.* **61**, 1342 (1964).

²¹³ V. Scatturin and R. Zannetti, *Ann. Chim. (Rome)* **49**, 68 (1959); *Chem. Abstr.* **53**, 13724 (1959).

²¹⁴ F. Pompa, V. Albano, P. L. Bellon, and V. Scatturin, *Ric. Sci., Parte 2: Sez. A* **8**, 1150 (1965); *Chem. Abstr.* **64**, 18555 (1966).

²¹⁵ I. Ambats and R. E. Marsh, *Acta Crystallogr.* **19**, 942 (1965).

B. QUANTUM MECHANICAL CALCULATIONS

During the last two decades numerous papers have been published dealing with molecular orbital calculations on oxazole and its derivatives, but due to the lack of relevant experimental data, a direct comparison between the theoretical and experimental results is difficult to make. In 1951, Orgel and his co-workers²¹⁶ were the first to calculate, within the framework of molecular orbital theory, the π -electron densities in the oxazole molecule, and C-2 was estimated to have the highest electron density. Since the MO theory was then in its early stages of development, the results are of qualitative importance only. More than a decade later Orloff and Fitts²¹⁷ calculated the π -electronic charge densities of oxazole by the semiempirical self-consistent field method (SCF-MO) using furan and imidazole type parameters for computation. In this and a subsequent publication²¹⁸ C-5 was suggested to have the largest electron density and it was predicted that electrophilic substitution for oxazole, reacting only as the neutral molecule, should occur at this position. Thus, these calculations supported the views of Katritzky and Lagowski,²¹⁹ while opposed to the speculations of Bassett, Brown, and Penfold,²²⁰ and of Orgel *et al.*²¹⁶ A more or less similar trend of π -electron density at various positions

TABLE I
CALCULATED π -ELECTRON DENSITIES OF OXAZOLE

O-1	C-2	N-3	C-4	C-5	Method	References
1.439	1.155	1.169	1.031	1.205	SCF-MO	217
1.368	1.186	1.185	1.020	1.241	SCF- LCAO- MO	218
1.842	0.982	1.124	0.951	1.101	HMO	221
1.679	0.944	1.277	0.994	1.106	SCF-CI	222
1.660	0.956	1.288	1.005	1.091	SCF-CI	222
1.755	0.973	1.166	1.029	1.077	CNDO-CI	222a

²¹⁶ L. E. Orgel, T. L. Cottrell, W. Dick, and L. E. Sutton, *Trans. Faraday Soc.* **47**, 113 (1951).

²¹⁷ M. K. Orloff and D. D. Fitts, *Tetrahedron* **19**, 1691 (1963).

²¹⁸ R. A. Sallavanti and D. D. Fitts, *Int. J. Quantum Chem.* **3**, 33 (1969).

²¹⁹ A. R. Katritzky and J. M. Lagowski, "Heterocyclic Chemistry," p. 221. Wiley, New York, 1960.

²²⁰ I. M. Bassett, R. D. Brown, and A. Penfold, *Chem. Ind. (London)*, 892 (1956).

was indicated by the calculations of Zurawski²²¹ and Kamiya²²² performed by the Hückel molecular orbital (HMO) method, and by the Pariser-Parr-Pople SCF method combined with configuration interaction, respectively. These results are summarized in Table I. Contradictory values of π -electron densities at C-4 and C-2 were obtained.

The energy calculated^{217, 218, 222} by the SCF methods for the first $\pi \rightarrow \pi^*$ spectral transition of oxazole agrees well with the experimental value¹⁰² of 6.05 eV. The first ionization potential of oxazole is calculated^{217, 218, 222} to be 9.2 eV.

Extended Hückel theory (EHT) calculations on oxazole suggest a significant polarization of the σ framework.²²³ This σ polarization appears to follow simple electronegativity considerations. The calculated π polarizations are independent of, and may be opposed to, the corresponding σ polarizations. A good correlation is observed between the total ($\sigma + \pi$) calculated electron densities²²³ and the experimental proton chemical shifts (see Section III,G).

Molecular geometries (bond lengths and bond angles) of oxazole have been estimated by various workers.^{218, 224-226} The results are summarized in Table II. Calculations of bond angles by O'Sullivan *et al.*²²⁵ indicate that bond angle variations are not due to bond distortion in the molecule; rather they seem consistent with other theoretical considerations. An angle of 104° for oxygen and nitrogen reflects the effect of the lone pair of electrons on the sp^2 orbital, while the carbon angles seem consistent with those found in similar molecules. An improved LCAO method gave similar bond angles for oxazole²²⁶ (see Table II).

Wave-mechanical calculations taking all electrons into account have also been performed on the oxazole molecule.^{227, 228} The SCF-MO-LCGO method (using floating Gaussian functions as a linear combination, so that p -, d -, and f -orbitals are also represented) has been used by Preuss and Janoschek²²⁷ to calculate the total energy and ionization energy of

²²¹ B. Zurawski, *Bull. Acad. Polon. Sci., Ser. Sci. Chim.* **14**, 481 (1966).

²²² M. Kamiya, *Bull. Chem. Soc. Jap.* **43**, 3344 (1970).

^{222a} Y. Ferré, R. Faure, and E. J. Vincent, *J. Chim. Phys. Physicochim. Biol.* **69**, 860 (1972).

²²³ W. Adam and A. Grimison, *Theor. Chim. Acta* **7**, 342 (1967).

²²⁴ R. D. Brown, B. A. W. Collier, and J. E. Kent, *Theor. Chim. Acta* **10**, 435 (1968).

²²⁵ P. S. O'Sullivan, J. De la Vega, and H. F. Hamerka, *Chem. Phys. Lett.* **5**, 576 (1970).

²²⁶ M. Roche, F. D'Amato, and M. Benard, *J. Mol. Struct.* **9**, 183 (1971).

²²⁷ H. Preuss and R. Janoschek, *J. Mol. Struct.* **3**, 423 (1969).

²²⁸ G. Berthier, L. Praud, and J. Serre, in "Quantum Aspects of Heterocyclic Compounds in Chemistry and Biochemistry," Proc. 2nd Int. Symp., 1969, (E. D. Bergmann and B. Pullmann, eds.), p. 40. Israel Acad., Jerusalem, 1970.

TABLE II
CALCULATED GEOMETRIES OF THE OXAZOLE MOLECULE

Bond lengths (Å)					Bond angles (degrees)					References
r_{12}	r_{23}	r_{34}	r_{45}	r_{51}	\angle_{512}	\angle_{123}	\angle_{234}	\angle_{345}	\angle_{451}	
1.39	1.46	1.40	1.41	—	—	—	—	—	—	218
1.36	1.30	1.37	1.36	1.36	102.4	115.0	104.8	107.9	109.9	224
1.36	1.33	1.39	1.35	1.36	104	114	104	109	109	225
1.35	1.31	1.39	1.35	1.36	104	116	101	111	107	226

TABLE III
CALCULATED DIPOLE MOMENTS OF OXAZOLE^a

μ_{σ} (D)	μ_{π} (D)	μ_{Total} (D)	Method	References
0.8	3.4	1.7	MO	216
1.36	2.09	1.80	MO-PPP	231
—	—	1.37	HMO	221
—	—	2.01	VE-SCF	230
—	—	1.89	VE-SCF	224
—	—	1.64	VE-SCF	224
1.13	1.35	1.58	Improved LCAO	226
1.17	1.33	1.69	Improved LCAO	226
—	—	1.38	CNDO/2	232
1.90	2.43	1.47	All-electron	228

^a Experimental value: (1) 1.4 D (from dielectric measurements).²¹⁶ (2) 1.50 ± 0.1 D (from Stark-effect measurements of its microwave spectrum).²³³

proton affinity. The values are -240.7 a. u. and 2.7 eV, respectively. Recently, the electrostatic molecular potentials arising from *ab initio* MO-LCAO-GTO (Gaussian-type orbital)-SCF wave functions for oxazole and some related heterocycles have been used to elucidate differences in reactivity of some sites towards electrophilic reagents.²²⁹ The results are in general accordance with experiment.

Several attempts have been made to compute the atomic charge distributions (both π -charges and total charges) and electric dipole moment^{216, 221, 224, 226, 228, 230-232} of oxazole, and thus to check the accuracies of the various MO procedures (see Table III). It is apparent from Table III that all-valence-electron calculations^{228, 232} including the atomic polarization terms yield dipole moments very close to the experimental value.^{216, 233}

Nitrogen-14 nuclear quadrupole coupling constants in oxazole have been calculated by using the complete neglect of differential overlap method (CNDO/2) including all the valence electrons,²³² and from *ab initio* molecular-orbital wave functions using Gaussian basis sets.²³⁴

²²⁹ G. Berthier, R. Bonaccorsi, E. Scrocco, and J. Tomasi, *Theor. Chim. Acta* **26**, 101 (1972).

²³⁰ R. D. Brown and B. A. W. Collier, *Theor. Chim. Acta* **7**, 259 (1967).

²³¹ D. W. Davies and W. C. Mackrodt, *Chem. Commun.*, 345 (1967).

²³² D. W. Davies and W. C. Mackrodt, *Chem. Commun.*, 1226 (1967).

²³³ W. C. Mackrodt, A. Wardley, P. A. Curnuck, N. L. Owen, and J. Sheridan, *Chem. Commun.*, 692 (1966).

²³⁴ E. Kochanski, J. M. Lehn, and B. Levy, *Chem. Phys. Lett.* **4**, 75 (1969).

TABLE IV
¹⁴N QUADRUPOLE COUPLING CONSTANTS (in MHz)

Calculated			Experimental ^a			References
χ_{aa}	χ_{bb}	χ_{cc}	χ_{aa}	χ_{bb}	χ_{cc}	
-4.29	+1.95	+2.34	-3.99	+1.58	+2.41	232
-4.99	+1.58	+3.41	—	—	—	234

^a From the microwave spectrum.²³³

The results of the former method agree rather well with the experiment²³³ (see Table IV) while those of the latter are only in moderate agreement. It is found that the largest component of $|\chi|$ lies approximately in the direction of the classically defined nitrogen lone pair.²³⁴

C. DIPOLE MOMENTS

The dipole moments of the oxazole molecule determined by dielectric²¹⁶ and Stark-effect measurements in the microwave spectrum²³³ are 1.4 and 1.5 ± 0.1 D, respectively. On the basis of small inertial defects in oxazole, Mackrodt *et al.*²³³ have concluded that the molecule is planar. There is a complete lack of data on the dipole moment of simple alkyl-substituted oxazoles. On the other hand, the values of the dipole moments of a number of aryl-substituted oxazoles have been reported (see Table V). As might be expected, a nitro substituent into the para position of a phenyl ring attached to oxazole increases the value of dipole moment by 2.0–3.5 D.

The relatively small magnitude of the dipole moment of oxazole itself, and of diphenyloxazoles, shows only small resonance contributions from some of the polar structures. The electron density distribution in 2,4-, 2,5-, and 4,5-diphenyloxazoles calculated by the LCAO-MO method indicates that these heterocycles do not contain a single π -electron system involving complete conjugation of the π -electrons of the C=N and C=C bonds with the p -electron pair on oxygen.²³⁵ However, vector calculations indicate considerable conjugation between substituents and π -electrons of the heterocycle through the phenyl ring.²³⁵

Changes in the electric dipole moments of 2-(1-naphthyl)-5-phenyloxazole and 2,5-bis(4-biphenyl)oxazole between the ground and excited states have been measured in various solvents by absorption and fluo-

²³⁵ A. E. Lutsikii, A. V. Shepel, O. P. Shvaika, N. P. Demchenko, and G. P. Klimisha, *Khim. Geterotsikl. Soedin.* **4**, 364 (1968); *Chem. Heterocycl. Compounds* **4**, 268 (1968).

TABLE V
DIPOLE MOMENTS OF OXAZOLES

Compound	D (Debye units)	References
Oxazole	1.4, 1.50	216, 233
2,4-Diphenyloxazole	1.29	235
2,5-Diphenyloxazole	1.55	235
4,5-Diphenyloxazole	1.85	235
2-Methyl-4,5-diphenyloxazole	1.7	235a
2-Bromomethyl-5-phenyloxazole	2.68	235
2- α -Bromoethyl-5-phenyloxazole	2.52	235
2-Biphenyl-5-phenyloxazole	1.65	235
2- <i>p</i> -Bromophenyl-5-phenyloxazole	1.87	235
2- <i>p</i> -Methoxyphenyl-5-phenyloxazole	1.92	235
2- <i>p</i> -Nitrophenyl-5-phenyloxazole	5.11	235
5- <i>p</i> -Nitrophenyl-2-phenyloxazole	3.56	235
5- <i>p</i> -Nitrophenyl-2- <i>p</i> -methoxyphenyloxazole	4.96	235
5-Biphenyl-2-phenyloxazole	1.95	235
2,5-Bis(4-biphenyl)oxazole	3.6	236
4-Bromo-2,5-diphenyloxazole	2.15	235
4-Iodo-2,5-diphenyloxazole	2.22	235
5-Iodo-2,4-diphenyloxazole	1.42	235
Benzoxazole	1.5	216

rescence spectroscopy.²³⁶ A similar measurement has been carried out by Kutsyna *et al.*²³⁷ on 2-phenyl-5-(4-dimethylaminophenyl)oxazole and compared with the calculated values.

D. THERMODYNAMIC DATA

The thermodynamic properties of oxazole for the ideal gaseous state assuming the harmonic oscillator-rigid rotator model have been calculated by Soptrajanov²³⁸ over the temperature range 298.16°–1000°K; and by Manley and Williams²³⁹ in the temperature range 50°–2000°K. At 25°C, the heat capacity of oxazole is 60.40 J K⁻¹ mole⁻¹; its heat content is 40.04 J K⁻¹ mole⁻¹; its free energy is 230.69 J K⁻¹ mole⁻¹; and the entropy

^{235a} P. F. Oesper, G. L. Lewis, and C. P. Smyth, *J. Amer. Chem. Soc.* **64**, 1130 (1942).

²³⁶ B. Bartoszewicz, P. Baluk, A. Chamma, and A. Kowski, *Bull. Acad. Pol. Sci., Ser. Sci., Math., Astron. Phys.* **19**, 175 (1971).

²³⁷ L. M. Kutsyna, V. M. Golovenko, L. D. Kornilovskaya, *Zh. Prikl. Spektrosk.* **15**, 466 (1971); *Chem. Abstr.* **76**, 13654 (1972).

²³⁸ B. Soptrajanov, *Croat. Chem. Acta* **40**, 79 (1968).

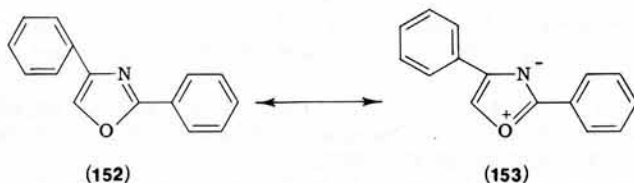
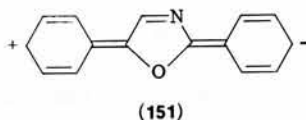
²³⁹ T. R. Manley and D. A. Williams, *Spectrochim. Acta, Part A* **24**, 361 (1968).

is $270.73 \text{ J K}^{-1} \text{ mole}^{-1}$ at 1 atm. The values found for oxazole are almost parallel to those of isoxazole, which is expected due to the close correspondence of the principal moments of inertia and the fundamental infrared frequencies of the two compounds.

E. ULTRAVIOLET AND FLUORESCENCE SPECTRA

The absorption maximum in the ultraviolet spectrum of oxazole appears at 205 nm ($\log \epsilon = 3.59$) which is at a longer wavelength than the first absorption maximum of benzene (λ_{max} 198 nm, $\log \epsilon \simeq 3.9$).^{102, 125, 160} Alkyl groups introduced at any position in the oxazole ring produce little or no effect in the position of the absorption maximum.^{91, 102} A phenyl group in conjugation with the double bond of the heterocycle causes the absorption band to shift towards longer wavelengths. Thus the absorption maxima of 2-, 4-, or 5-phenyloxazoles (with or without alkyl substituents at other positions) lie at 243–267 nm.^{102, 240} The observation that the 2- or 5-phenyloxazoles absorb at approximately 20 nm higher wavelength than the 4-phenyloxazoles can be attributed to the formal conjugation of the phenyl ring with the two double bonds in the oxazole nucleus.

Brown and Ghosh²⁴⁰ have used ultraviolet spectroscopy to study the nature of the bonding in diphenyloxazoles. The spectrum of 2,5-diphenyloxazole shows two main peaks, of which the high-intensity one at 314 nm ($\log \epsilon$ 4.34) is considered to arise from an extended conjugation as in structure **151**, cf. *p*-terphenyl, 2,5-diphenylfuran, and 2,5-diphenyl-1,3,4-oxadiazole.²⁴¹ The absence of such a high-intensity peak above 276 nm in the spectrum of 2,4-diphenyloxazole (**152**) suggests that canonical structures such as **153** contribute little to the oxazole resonance, and hence to the conclusion that an oxazole is more like a conjugated diene than a fully aromatic system.²⁴⁰



²⁴⁰ D. J. Brown and P. B. Ghosh, *J. Chem. Soc. B*, 270 (1969).

²⁴¹ H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," p. 274. Wiley, New York, 1962.

A simple MO calculation of the longest-wavelength band in the absorption spectra of oxazole and its mono- and diphenyl-substituted derivatives has been performed by Balaban *et al.*²⁴²; their results are in agreement with experimental data.

Introduction of a phenyl group into the 4-position of 2,5-diphenyloxazole produces a slight bathochromic shift and lowered intensities for both absorption and fluorescence spectra.²⁴³ The spectrum of 4- or 5-benzyl-substituted oxazoles shows λ_{\max} at 250–270 nm ($\log \epsilon$ 2.1–2.6).¹⁰²

Intense peaks appear in the ultraviolet spectrum when a carbonyl function is conjugated with the oxazole ring as in the oxazole carboxylic

TABLE VI

ULTRAVIOLET ABSORPTION SPECTRAL DATA OF SOME SIMPLE OXAZOLES

Oxazole	λ_{\max} (nm)	ϵ (log ϵ)	λ_{\max} (nm)	ϵ (log ϵ)	References
Unsubstituted	205	(3.59)	—	—	125, 160
4-Me-5-CH ₂ Cl	223.5	(3.87)	—	—	91
4-Me-5-CH ₂ CH ₂ Br	220	(3.78)	—	—	91
2,4-Me ₂ -5-CH ₂ CH ₂ Cl	218.5	(3.83)	—	—	91
2-Ph	263	16,290	—	—	240
4-Ph	243	17,420	—	—	101, 102, 240
5-Ph	267	19,370	261	19,800	240
5-Me-4-Ph	247	(4.18)	—	—	101, 102
2,5-Me ₂ -4-Ph	247	(4.06)	—	—	101, 102
4-Me-5-Ph	265	(4.23)	—	—	101, 102
2,4-Me ₂ -5-Ph	264	(4.29)	—	—	101, 102
2,4-Ph ₂	276	17,200	232	17,500	240
2,5-Ph ₂	314	22,080	244	12,100	240, 243
4,5-Ph ₂	275	(4.09)	220	(4.27)	243a
2-Ph-4-CH ₂ Cl	266	13,300	216.5	2,100	389
2-Ph-4-CH ₂ Br	268	15,900	210	13,150	389
2-Ph-4-CH ₂ OH	268	11,600	218	2,880	389
2-Ph-4-CH ₂ CN	264.5	14,000	—	—	389
2-Ph-4-NCO	277	8,500	—	—	389
4-COOEt	214	(3.88)	—	—	125
4,5-(COOEt) ₂	241.5	(3.95)	—	—	125
4,5-(COOMe) ₂	241.5	(3.95)	—	—	125

²⁴² Z. Simon and A. T. Balaban, *Rev. Roum. Chim.* **8**, 199 (1963).

²⁴³ D. G. Ott, F. N. Hayes, E. Hansbury, and V. N. Kerr, *J. Amer. Chem. Soc.* **79**, 5448 (1957).

^{243a} R. Gompper and H. Herlinger, *Chem. Ber.* **89**, 2816 (1956).

esters,^{61, 112, 125} carboxylic acids,^{38, 147} carboxamides,^{199, 200} and acetyloxazoles.¹⁴⁷ Ultraviolet spectral data for 5-alkoxyoxazoles^{66, 69} and 5-aminooxazoles^{61, 112, 198, 199, 208, 244} have also been recorded. Table VI lists ultraviolet absorption spectral data for a number of simple oxazoles.

Ultraviolet absorption spectroscopy has been used to determine isomeric product ratios,¹⁰¹ to estimate the position of the thione-thiol equilibrium in oxazoline-2 (3*H*)-thiones,²⁴⁵ to study the mechanism of the isomerization of 5-aminooxazoles to α -acylaminonitriles,²⁴⁴ and also for the quantitative determination of 4-methyl-5-propoxyoxazole.²⁴⁶ Berلمان,²⁴⁷ from a study of emission spectrograms, has shown that transient excited dimers are formed by concentrated solutions of 2,5-diphenyloxazole in *p*-xylene.

Of the oxazoles studied by spectrophotometry, perhaps the most extensively observed are the 2,5-diaryl derivatives, because it is well known that 2,5-diaryloxazoles possess the best scintillation characteristics. Moreover, since absorption and fluorescence spectra are both important for scintillators, a huge compilation of such data has been made available in the last two decades.^{22, 41, 47-50, 243, 248-253} This property of oxazoles has, in fact, been the subject of several monographs^{241, 254-257} in the past, and therefore it is not discussed at any length in this review.

²⁴⁴ G. Kille and J. P. Fleury, *Bull. Soc. Chim. Fr.*, 4631 (1968).

²⁴⁵ G. Kjellin and J. Sandstrom, *Acta Chem. Scand.* **23**, 2888 (1969).

²⁴⁶ V. M. Svetlaeva, V. V. Mishchenko, and I. M. Kustanovich, *Khim.-Farm. Zh.* **5**, 49 (1971); *Chem. Abstr.* **75**, 67542 (1971).

²⁴⁷ I. B. Berلمان, *J. Chem. Phys.* **34**, 1083 (1961).

²⁴⁸ F. N. Hayes, V. N. Kerr, D. G. Ott, E. Hansbury, and B. S. Rogers, *U.S. At. Energy Comm. LA-2176* (1958).

²⁴⁹ M. D. Barnett, D. H. Daub, F. N. Hayes, and D. G. Ott, *J. Amer. Chem. Soc.* **82**, 2282 (1960).

²⁵⁰ G. Drefahl and U. Engelmann, *Chem. Ber.* **93**, 492 (1960); G. Drefahl and K. Winnefeld, *J. Prakt. Chem.* **29**, 72 (1965).

²⁵¹ Yu. N. Panov, N. A. Androva, and M. M. Koton, *Opt. Spektrosk.* **7**, 29 (1959); *Chem. Abstr.* **54**, 23814 (1960).

²⁵² L. M. Kutsyna and E. T. Verkhovtseva, *Opt. Spektrosk.* **12**, 785 (1962); *Chem. Abstr.* **57**, 15960 (1962).

²⁵³ V. A. Kornienko, L. M. Kutsyna, and V. G. Vlasov, *Opt. Spektrosk.* **32**, 1234 (1972); *Chem. Abstr.* **77**, 82097 (1972).

²⁵⁴ I. B. Berلمان, "Handbook of Fluorescence Spectra of Aromatic Molecules." Academic Press, New York, 1965.

²⁵⁵ J. B. Birks, "The Theory and Practice of Scintillation Counting." Pergamon, Oxford, 1967.

²⁵⁶ D. M. Hercules (ed.), "Fluorescence and Phosphorescence Analysis: Principles and Applications." Wiley (Interscience), New York, 1966.

²⁵⁷ G. G. Guilbault (ed.), "Fluorescence: Theory, Instrumentation, and Practice." Arnold, London, 1967.

F. INFRARED AND RAMAN SPECTRA

Assignments of the absorption frequencies of oxazole^{125,258,259} in the infrared region fall into three main regions: 600–1260 cm^{-1} (modes involving the oxazole nucleus, and that involving the CH, i.e., in-plane and out-of-plane bending vibrations), 1330–1550 cm^{-1} (aromatic C—C and C—N bonds), and 3080–3170 cm^{-1} (C—H stretching vibrations). Borello, Zecchina, and Appiano²⁵⁸ studied the infrared spectra of oxazole in the gaseous and liquid states at room temperature between 4000 and 600 cm^{-1} . On the basis of similarity to the spectrum of isoxazole and its published assignments, they made a plausible spectral assignment for the oxazole molecule. They also concluded that oxazole belongs to the C_s point group (assuming a planar structure) and that it can be considered as a nearly symmetric top.

The infrared and Raman spectra of oxazole and thiazole have been measured in the vapor, liquid, and solid states as well as in solution, and a complete assignment of the normal modes of vibration has been made.²⁵⁹ Once again, a planar structure for oxazole has been assumed in analogy with the then-known planar structure of thiazole. Despite the difference in approaches of the two groups of workers,^{258,259} the vibrational assignments of oxazole (a total of 18 normal modes, all infrared- and Raman-active) agree almost completely. PR branch separations of band envelopes produced by the oxazole molecule have been calculated and compared with the experimental values.²⁶⁰

Infrared spectra of 4-methyloxazole and 2,4-dimethyloxazole for the gaseous and liquid states, and of liquid 2-*n*-hexyl-5-methyloxazole, have been measured at room temperature between 4000 and 600 cm^{-1} . A comparison with the spectra of oxazole and considerations of the rotational envelopes has allowed a plausible assignment of the absorption bands with reasonable success.²⁶¹ Examination of the infrared spectra in the solid state of 2,4-dimethyl-, 2-methyl-4-phenyl-, and 2-methyl-4,5-diphenyloxazoles, and various benzoxazoles shows regularities in the 1660–1500 cm^{-1} region. Absorption bands at 1660–1600 cm^{-1} and 1585–1500 cm^{-1} have been assigned to the vibrations arising from the heterocyclic ring system.²⁶²

²⁵⁸ E. Borello, A. Zecchina, and A. Appiano, *Spectrochim. Acta* **22**, 977 (1966).

²⁵⁹ G. Sbrana, E. Castellucci, and M. Ginanneschi, *Spectrochim. Acta, Part A* **23**, 751 (1967).

²⁶⁰ W. A. Seth Paul and G. Dijkstra, *Spectrochim. Acta, Part A* **23**, 2861 (1967).

²⁶¹ E. Borello, A. Zecchina, and A. Appiano, *Spectrochim. Acta, Part A* **23**, 1335 (1967).

²⁶² P. Bassignana, C. Cogrossi, and M. Gandino, *Spectrochim. Acta* **19**, 1885 (1963).

The infrared spectra (recorded in carbon tetrachloride and carbon disulfide solutions or mulls) of more than 25 2-aryl-5-phenyloxazoles have been reproduced, tabulated, and discussed by Hayes *et al.*²⁶³

Infrared absorption spectral data for several oxazole derivatives,^{85,90} including alkyl-^{98,125} and aryl-^{263,264} substituted oxazoles, 2-amino- and substituted-amino derivatives^{109,112,135}, 5-amino^{179,198-201} and 5-alkoxy-oxazoles,⁶⁶ carboxylic acids,^{112,147} esters,^{125,179,184} carboxamides,^{199,200} 4-acetyloxazoles,¹⁴⁷ halogenoalkyl oxazoles,⁹¹ oxazolines,²⁶² and benzoxazoles²⁶² have been reported.

G. NUCLEAR MAGNETIC RESONANCE SPECTRA

The proton magnetic resonance spectrum of oxazole (in carbon tetrachloride) is relatively simple and shows two one-proton broad singlets at $\delta = 7.84$ ppm and 7.12 ppm (assigned to the 2-H and 4-H, respectively), and a one-proton triplet centered at $\delta = 7.66$ ppm (assigned to the 5-H). The 5-H atom is coupled equally to H-2 and H-4 ($J_{2,5} = J_{4,5} \approx 0.9$ Hz) and then these later proton bands are broadened by nitrogen coupling.²⁶⁵ These coupling constants are slightly lower than the corresponding values in 1-methylimidazole²⁶⁶ ($J_{4,5} = 1.0$ Hz) and substantially lower than in thiazole^{267,268} ($J_{2,5} = 1.9$ Hz, $J_{4,5} = 3.2$ Hz), thereby indicating greater bond polarization by the strongly electronegative oxygen atom than by nitrogen or sulfur.²⁶⁹ The apparent lack of 2,4-coupling is attributed to nitrogen perturbation.²⁴⁰

Chemical shift data for a number of simple oxazoles are listed in Table VII.

The progressive introduction of methyl groups into oxazole causes the expected upfield shift of proton signals relative to those of the parent; electron-withdrawing substituents cause a shift in the opposite direction. These substituent effects, in general, appear to be transmitted inductively.²⁴⁰ A phenyl group in the 4- or 5-position has little effect on the

²⁶³ V. L. Koenig, F. N. Hayes, B. S. Rogers, and J. D. Perrings, *U.S. At. Energy Comm. AECU-2778* (1953).

²⁶⁴ L. L. Nagornaya, O. A. Gunder, and V. S. Koba, *Prom. Khim. Reaktivov Osobo Chist. Veshchestv* **8**, 26 (1967); *Chem. Abstr.* **69**, 32336 (1968).

²⁶⁵ H. A. Staab, H. Irngartinger, A. Mannschreck, and M.-Th. Wu, *Liebigs Ann. Chem.* **695**, 55 (1966).

²⁶⁶ G. B. Barlin and T. J. Batterham, *J. Chem. Soc. B*, 516 (1967).

²⁶⁷ B. Bak, J. T. Nielsen, J. Rastrup-Andersen, and M. Schottlander, *Spectrochim. Acta* **18**, 741 (1962).

²⁶⁸ A. Taurins and W. G. Schneider, *Can. J. Chem.* **38**, 1237 (1960).

²⁶⁹ C. N. Banwell and N. Sheppard, *Disc. Faraday Soc.* **34**, 115 (1962).

TABLE VII

CHEMICAL SHIFTS (δ , ppm) OF AROMATIC PROTONS AND METHYL PROTONS OF SOME SIMPLE OXAZOLES^a

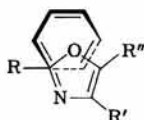
Oxazole	2-H	4-H	5-H	2-CH ₃	4-CH ₃	5-CH ₃	References
Unsubstituted	7.95	7.09	7.69	—	—	—	240, 265, 271
2-Me	—	6.82	7.41	2.37	—	—	240, 271
4-Me	7.77	—	7.27	—	2.11	—	240, 270, 271
2,4-Me ₂	—	—	7.14	2.22	2.06	—	240
2,5-Me ₂	—	6.42	—	2.29	—	2.22	240
4,5-Me ₂	7.69	—	—	—	2.08	2.24	135, 240
4-Me-5-Et	7.71	—	—	—	2.12	—	98
4-Me-5-Pr	7.72	—	—	—	2.16	—	98
4-Me-5-Bu ⁱ	7.70	—	—	—	2.14	—	98
4,5-Pr ₂	7.54	—	—	—	—	—	265, 272
2,4,5-Me ₃	—	—	—	2.28	1.96	2.15	240, 271
4-COOEt	8.20	—	7.91	—	—	—	240
4-CONH ₂	8.29	—	7.87	—	—	—	240
2-Me-4-COOEt	—	—	8.17	2.50	—	—	240
4-Me-5-Ac	7.95	—	—	—	2.49	—	240
4-Me-5-CN ^b	8.41	—	—	—	2.40	—	240
4-Me-5-CONH ₂	7.82	—	—	—	2.51	—	240
4-Me-5-COOMe	7.99	—	—	—	2.46	—	240
4-Me-5-COOEt	7.96	—	—	—	2.47	—	240
5-Me-2-COOEt	—	6.97	—	—	—	2.43	107
2,4-Me ₂ -5-Ac	—	—	—	2.45	2.35	—	240
2,4-Me ₂ -5-COOEt ^c	—	—	—	2.55	2.40	—	240
2,5-Me ₂ -4-Ac	—	—	—	2.40	—	2.35	240
2,5-Me ₂ -4-COOEt	—	—	—	2.50	—	2.23	240
4,5-Me ₂ -2-MeO	—	—	—	3.92 ^d	1.90	2.09	156
2-Ph-4-Me-5-MeO	—	—	—	—	2.07	3.94 ^d	159

^a Solvents are either CCl₄ or CDCl₃ unless stated otherwise.^b MeOD.^c D₂O.^d Methoxyl absorption.

chemical shift of 2-H but a *p*-nitrophenyl group, especially at the 4-position, produces an appreciable downfield shift of the 2-H signal. The presence of electron-withdrawing or electron-releasing groups has been shown to have little, if any, effect on the coupling constants.

Replacement of carbon tetrachloride by deuterium oxide as solvent causes a greater downfield shift (approx. ≥ 0.3 ppm) in signals for H-2 and H-5 than in that for H-4 (~ 0.2). Change of solvent has a relatively

small effect on the chemical shift of methyl protons, the least being on the 4-methyl protons.^{240, 270} Benzene-induced solvent shifts in the nuclear magnetic resonance spectra of several substituted oxazoles can be interpreted as indicating that benzene complexes near the oxygen atom of the oxazole nucleus and forms a 1:1 solute-solvent collision complex of the type **154**.²⁷¹



(154)

Protonation has virtually no effect on the coupling constants of oxazoles but causes considerable changes in the chemical shift for the ring protons. Such changes for H-2 are particularly marked compared with those in other related heterocycles;^{240, 265-267, 270} the changes for H-4 and H-5 are less pronounced and quite close. Brown and Ghosh²⁴⁰ consider this as consistent with part of the positive charge residing on the oxygen atom in such oxazolium cations. The very low chemical shifts for the 2-H in oxazolium ions is attributed to an unusually high deshielding of this proton and it is therefore an unusually acidic aromatic hydrogen.²⁷⁰

The chemical shifts of H-2 in oxazolium salts have been shown to be very strongly solvent-dependent; it was conspicuous that the transition from less polar solvents to methanol effected a shift to higher field strength, while with oxazoles a shift in the reverse direction was observed.²⁷²

The use of PMR spectroscopy has permitted the investigation of hydrogen-deuterium exchange phenomena in oxazoles and oxazolium salts. Staab and his co-workers^{265, 272} have found that the rate of exchange of the 2-proton in 4,5-disubstituted oxazolium methiodides is faster than in the corresponding bases by several powers of 10. Thus, the half-life time for the deuteration of 4,5-dipropylloxazole in methanol-*d* is 600 minutes (at 60°), while the 2-position of the corresponding methiodide is completely deuterated after 3 minutes at 37°C.

In order to study the nature of activated hydrogens in compounds related to thiamine (vitamin B₁), Hafferl, Lundin, and Ingraham²⁷³

²⁷⁰ P. Haake and W. B. Miller, *J. Amer. Chem. Soc.* **85**, 4044 (1963).

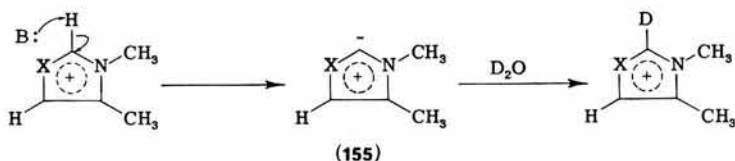
²⁷¹ J. H. Bowie, P. F. Donaghue, and H. J. Rodda, *J. Chem. Soc. B*, 1122 (1969).

²⁷² H. A. Staab, M.-Th. Wu, A. Mannschreck, and G. Schwalbach, *Tetrahedron Lett.*, 845 (1964).

²⁷³ W. Hafferl, R. Lundin, and L. L. Ingraham, *Biochemistry* **2**, 1298 (1963).

have measured the rate of exchange of H-2 with deuterium in 3,4-dimethyloxazolium iodide at pD 3.8–4.7 in 0.1 *N* acetate-*d* buffer. The observation, by NMR that oxazolium salts exchange at the 2-position faster than the corresponding thiazolium salts²⁷³ led Pullman *et al.*²⁷⁴ to revise their previous calculations of net π -electron distribution in these systems.²⁷⁵ The large net positive charge on C-2 in 4-methyloxazolium and 3,4-dimethyloxazolium ions is considered to effectively polarize the C-2—H bond in such a way as to remove the electrons from H-2. A reasonable agreement between the calculated π -charge distribution and observed NMR chemical shifts has also been found.²⁷⁴

Haake, Bausher, and Miller²⁷⁶ in a similar study on the rates of exchange of 2-hydrogens in 3,4-dimethyloxazolium, 3,4-dimethylthiazolium, and 1,3,4-trimethylimidazolium ions, found relative second-order rate constants of $10^{5.5}:10^{3.5}:1$, respectively. This indicates that the 3,4-dimethyloxazolium ion exchanges its 2-proton with deuterium 100 times faster than the corresponding thiazolium ion, which in turn exchanges about 3000 times faster than the 1,3,4-trimethylimidazolium ion. The exchange reaction is believed to occur through the ylide (155, X = O, S, or NCH₃).



Nuclear magnetic resonance spectroscopy has been used to determine the isomer distribution in reaction products,^{98,135} to determine substituent positions,²⁷⁷ and generally to study structural problems.^{109,156,201} NMR data for a number of 2- and 5-aminooxazoles and their N-substituted derivatives have also been recorded.^{107,135,198–201} The observed proton chemical shifts of oxazole and other heteroaromatic compounds have been used to obtain estimates of the electron distribution in these systems.²⁷⁸

Carbon-13 magnetic resonance studies have been made on 4-methyloxazole and its onium ions.^{270,276,279} The ¹³C—H coupling constants are

²⁷⁴ R. L. Collin and B. Pullman, *Arch. Biochem. Biophys.* **108**, 535 (1964).

²⁷⁵ B. Pullman and C. Spanjaard, *Biochim. Biophys. Acta* **46**, 576 (1961).

²⁷⁶ P. Haake, L. P. Bausher, and W. B. Miller, *J. Amer. Chem. Soc.* **91**, 1113 (1969).

²⁷⁷ G. Kjellin and J. Sandstrom, *Spectrochim. Acta, Part A* **25**, 1865 (1969).

²⁷⁸ P. J. Black, R. D. Brown, and M. L. Heffernan, *Aust. J. Chem.* **20**, 1305 (1967).

²⁷⁹ L. P. Bausher, Ph.D. Thesis, University of California, Los Angeles (1967); *Diss. Abstr. B* **28**, 565 (1967).

unusually large in both the free base and the onium ions, especially for H-2 in the protonated 4-methyloxazole ($J_{^{13}\text{C}-2\text{H}} = 247 \text{ Hz}$) and in 3,4-dimethyloxazolium ion ($J_{^{13}\text{C}-2\text{H}} = 246 \text{ Hz}$). These values lie in the same range as those for acetylenic hydrogens, nearly as large as any $^{13}\text{C}-\text{H}$ coupling constant yet observed.^{270,276} Once again, this reflects the high acidity of H-2 in these systems. No experimental data are available for $^{13}\text{C}-\text{H}$ coupling constants in oxazole; however, the calculated values for the 2-, 4-, and 5-positions are 227.0, 200.5, and 208.5 Hz, respectively.²⁸⁰

The nitrogen-14 nuclear magnetic resonance spectra of several azoles (including oxazole) and their benzo derivatives show a linear relationship between the chemical shifts and the SCF-PPP-MO π -charge densities.²⁸¹ The ^{14}N chemical shift of oxazole is $124 \pm 1 \text{ ppm}$ (in carbon tetrachloride) at high field relative to internal nitromethane.²⁸¹ A value of $125 \pm 10 \text{ ppm}$ has been reported for the ^{14}N chemical shift in 2,5-diphenyloxazole relative to ^{14}N of NO_3^- in ammonium nitrate.²⁸²

H. MASS SPECTROMETRY

The first published account of the mass spectrometry of isomeric diphenyloxazoles was initiated in an attempt to establish the structure of a new oxazole alkaloid.²⁸³ A detailed study of the mass spectra of a variety of alkyl- and arylloxazoles was not reported until recently.^{284,285} The mass spectrum of oxazole itself is typical of an unsubstituted aromatic compound inasmuch as the molecular ion (m/e 69) constitutes the base peak. The major fragment ions occur at $M - 1$, $M - 27$ ($M - \text{HCN}$), $M - 28$ ($M - \text{H}_2\text{CN}$ and/or $M - \text{CO}$) and $M - 29$ ($M - \text{CHO}$).²⁸⁴

The mass spectra of isomeric alkylloxazoles are distinctive and exhibit characteristic fragmentation patterns; in this respect they are akin to those of the corresponding pyridines. One of the most intriguing features of the spectra is the marked tendency for many of the oxazoles to eliminate carbon monoxide from the molecular ion, typically by the pathway shown in Scheme 5.²⁸⁴

²⁸⁰ K. Tori and T. Nakagawa, *J. Phys. Chem.* **68**, 3163 (1964).

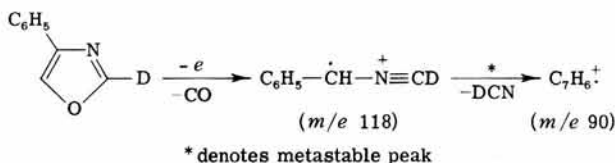
²⁸¹ M. Witanowski, L. Stefaniak, H. Januszewski, Z. Grabowski, and G. A. Webb, *Tetrahedron* **28**, 637 (1972).

²⁸² D. Herbison-Evans and R. E. Richards, *Mol. Phys.* **8**, 19 (1964).

²⁸³ W. D. Crow, J. H. Hodgkin, and J. S. Shannon, *Aust. J. Chem.* **18**, 1433 (1965).

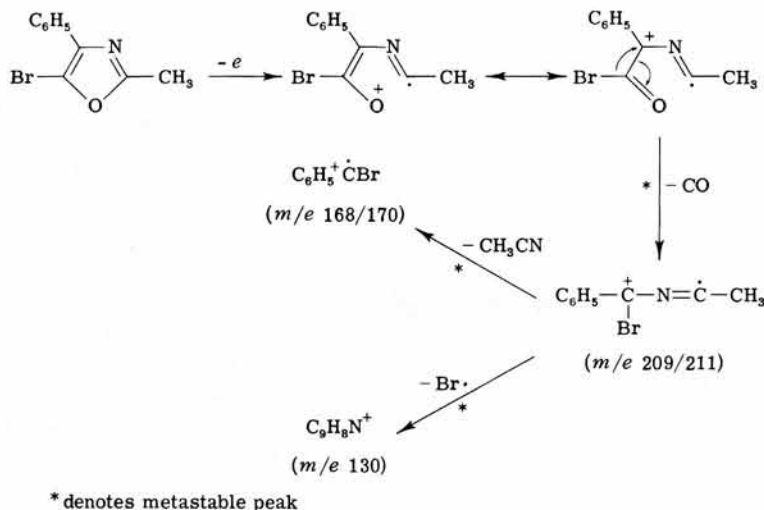
²⁸⁴ J. H. Bowie, P. F. Donaghue, H. J. Rodda, R. G. Cooks, and D. H. Williams, *Org. Mass Spectrom.* **1**, 13 (1968).

²⁸⁵ J. H. Bowie, P. F. Donaghue, H. J. Rodda, and B. K. Simons, *Tetrahedron* **24**, 3965 (1968).



Scheme 5

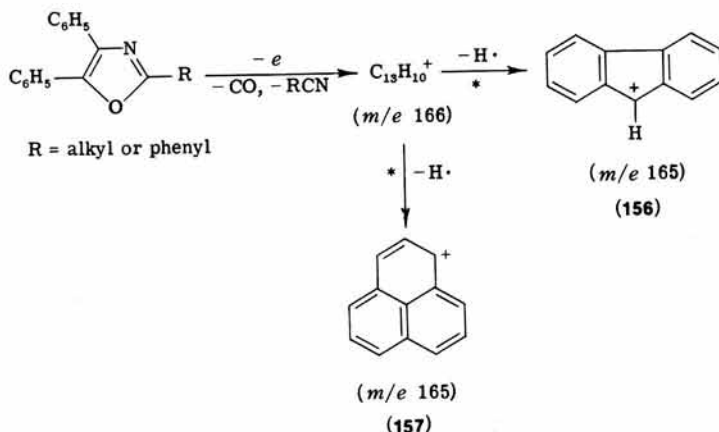
The loss of carbon monoxide from the molecular ions of 2,5-disubstituted oxazoles has been suggested to occur with ring-opening and subsequent (or associated) migration of the C-5 substituent (e.g., bromine) to the C-4 position. Such 1,2-shifts to carbonium ion centers generated upon electron impact are well established (Scheme 6).



Scheme 6

Bond-forming reactions also occur during the fragmentation of 2,5- and 4,5-diphenyloxazoles as evidenced by abundant ions of mass m/e 165 and 166 in their spectra. The m/e 166 ($\text{C}_{13}\text{H}_{10}^+$) formally originates from the two phenyl rings and one C atom of the oxazole nucleus. The facile loss of a hydrogen atom is almost certainly associated with skeletal rearrangement to the fluorenyl cation (156) or to the phenalenium cation (157) (Scheme 7).²⁸⁴

The formation of the fluorenyl cation (156) in the spectra of diphenyloxazoles has been noted previously²⁸³ and a mechanism has been proposed. It has been suggested²⁸⁵ that the formation of 156 from 2,5-diphenyloxazole



Scheme 7

is energetically more favorable than its formation from 4,5-diphenyloxazole, and that the bond formation does not occur between the 2- and 4-substituents because of the relatively small abundance of **156** in the mass spectrum of 2,4-diphenyloxazole.

Deuterium-labeling experiments²⁸⁴ indicate that D atoms inserted into the oxazole nucleus, or incorporated in methyl groups attached to the oxazole nucleus, are not randomized with H atoms at other nuclear positions prior to the major fragmentation, in contrast to what occurs with simple alkyl benzenes. This technique has allowed the detection from the spectrum of 2,4,5-triphenyloxazole of two alternative rearrangement pathways.²⁸⁵ Recently, a *p*-fluoro-labeling study²⁸⁶ found partial scrambling before fragmentation in 2-*p*-fluorophenyl-4,5-diphenyloxazole.

A tentative correlation between the mass spectral fragmentation of 3,5-diphenylisoxazole, 2-phenyl-3-benzoyl-1-azirine, and 2,5-diphenyloxazole, and their photochemical behavior has been suggested by Japanese workers.²⁸⁷

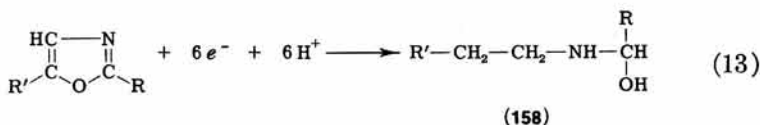
I. POLAROGRAPHY

Polarographic data (half-wave potentials, diffusion current constants, etc.) on several oxazole derivatives have been obtained by Bezuglyi

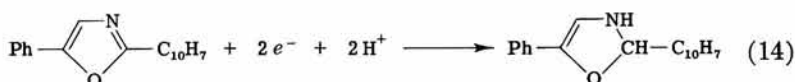
²⁸⁶ M. M. Bursey and R. L. Nunally, *J. Org. Chem.* **37**, 3032 (1972).

²⁸⁷ H. Nakata, H. Sakurai, H. Yoshizumi and A. Tatematsu, *Org. Mass Spectrom.* **1**, 199 (1968).

*et al.*²⁸⁸⁻²⁹² Reduction of the majority of the 2,5-diaryloxazoles on a dropping mercury electrode, using tetraethylammonium iodide as the supporting electrolyte in 92% methanol, requires six electrons for the reduction of the C=N, C=C, and C—O bonds. The electrochemical reduction process for these oxazoles is suggested to proceed as shown in Eq. (13). The product (158) would, however, be expected to be hydrolyzed easily to an amine and an arylaldehyde.



Unlike the other 2,5-diaryloxazoles, 2-(1-naphthyl)-5-phenyl- and 2-(2-naphthyl)-5-phenyloxazoles consume only two electrons per molecule for reduction [Eq. (14)], giving 4-oxazoline derivatives as the product.²⁸⁹ The 2-methyl analog was not reduced on a mercury electrode.²⁸⁸



Moreover, 2,4- and 4,5-diphenyloxazoles require only four electrons for reduction of the oxazole nucleus without the ring-opening. Polarographic investigations of halo- and mercury-substituted oxazoles,²⁹⁰ and vinyl-²⁹¹ and nitro-²⁹³ substituted diaryloxazoles have also been reported. The half-wave potentials for oxazole derivatives have been noted to be pH- and temperature-dependent.^{289,293}

Greig and Rogers²⁹⁴ studied the electrochemical behavior of 2,5-diphenyloxazole and 2-(1-naphthyl)-5-phenyloxazole in an aprotic solvent,

²⁸⁸ V. D. Bezuglyi and N. P. Shimanskaya, *Zh. Obshch. Khim.* **31**, 3160 (1961); *J. Gen. Chem. USSR* **31**, 2948 (1961).

²⁸⁹ V. D. Bezuglyi, N. P. Shimanskaya, and E. M. Peresleni, *Zh. Obshch. Khim.* **34**, 3540 (1964); *J. Gen. Chem. USSR* **34**, 3588 (1964).

²⁹⁰ N. P. Shimanskaya, G. P. Klimisha, O. P. Shvaika, and V. D. Bezuglyi, *Khim. Geterotsikl. Soedin.* **3**, 596 (1967); *Chem. Heterocycl. Compounds* **3**, 481 (1967).

²⁹¹ T. A. Alekseeva and V. D. Bezuglyi, *Zh. Obshch. Khim.* **37**, 1943 (1967); *J. Gen. Chem. USSR* **37**, 1845 (1967).

²⁹² V. D. Bezuglyi, N. P. Shimanskaya, and I. F. Mikhailova, *Khim. Geterotsikl. Soedin.* **4**, 26 (1968); *Chem. Heterocycl. Compounds* **4**, 21 (1968).

²⁹³ F. Makkay, C. Makkay, and M. Ionescu, *Stud. Univ. Babes-Bolyai, Ser. Chem.* **15**, 119 (1970); *Chem. Abstr.* **75**, 14225 (1971).

²⁹⁴ W. N. Greig and J. W. Rogers, *J. Electrochem. Soc.* **117**, 1141 (1970).

TABLE VIII
BASIC pK VALUES OF SUBSTITUTED
OXAZOLES^{a, b}

Substituent	pK_a
4-Me	1.24
2,4-Me ₂	2.91
4,5-Me ₂	2.05
2,4,5-Me ₃	3.56
4,5-(CH) ₄ ^c	-0.5
4-Ph	-1.21
5-Ph	0.26
5- <i>p</i> -ClC ₆ H ₄	0.16
5- <i>p</i> -O ₂ N.C ₆ H ₄	-0.19
5- <i>p</i> -MeO.C ₆ H ₄	0.70
4-Me-5-Ac	-0.97
Oxime deriv.	0.18
4-Me-5-COOEt	-0.89 ^d
4-Me-5-COOMe	-1.00
4-Me-5-Ph	1.09
4-Me-5- <i>p</i> -O ₂ N.C ₆ H ₄	0.39
2,4-Me ₂ -5-Ac	0.21
2,4-Me ₂ -5-COOEt	0.28
2,4-Me ₂ -5-Ph	2.45
2,4-Me ₂ -5- <i>p</i> -O ₂ N.C ₆ H ₄	1.69
2,5-Me ₂ -4-Ac	0.20
Oxime deriv.	1.28
2-Me-4-COOEt	-0.89
2,5-Me ₂ -4-COOEt	0.15

^a All values have been taken from Brown and Ghosh,²⁴⁰ except as quoted.

^b Measurements in aqueous media at 20° spectrometrically.

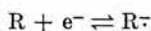
^c Benzoxazole. From Snyder and Buell.^{299a}

^d Haake and Bausher³⁰⁰ have reported a value of +0.83 from potentiometric titration.

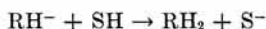
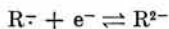
dimethylformamide, at platinum and mercury electrodes in the presence and absence of proton donors. Both compounds are reduced via two polarographic steps. The first is a reversible one-electron transfer producing a stable anion radical. The second is a reversible one-electron transfer followed by rapid protonation of the dianion. The resulting protonated

species undergo a slow irreversible reaction, finally, to give the long-term electrolysis product.

First wave



Second wave



where R is the substituted oxazole and SH is a proton source.

A study of the influence of the proton donor hydroquinone on the polarographic reduction of a series of phenyl- and naphthyl-substituted oxazoles in dimethyl formamide suggest that they are reduced at high proton donor to compound ratios.²⁹⁵ The polarographic behavior of 2,5-diphenyloxazole hydrobromide in DMF has also been studied.²⁹⁶

J. ACID-BASE STRENGTH

Until recently it was thought, on the basis of their solubility in aqueous acid and the stability of the oxazole hydrochlorides towards hydrolysis, that the oxazoles and pyridines are bases of comparable strength.¹ This suggestion can no longer be accepted in view of the pK_a values (see Tables VIII and IX) obtained by Brown and Ghosh,²⁴⁰ which indicate that oxazoles are about 10^4 times weaker bases than the corresponding pyridines.

The pK_a value of oxazole itself has been determined²⁴⁰ by the chemical shifts of H-2 in acidic media and is 0.8 ± 0.2 at 33°C . The feebly basic strength of oxazole relative to thiazole (pK_a 2.53),²⁹⁷ pyridine (5.23),²⁹⁷ or 1-methylimidazole (7.33)²⁹⁸ is attributed primarily to the powerful inductive effect of the electronegative oxygen atom. This effect, evident in isoxazole (pK_a -2.03),^{240, 299} is clearly more important than any base-strengthening effect from delocalization of the oxygen lone pair in oxazole.

²⁹⁵ S. L. Smith, L. D. Cook, and J. W. Rogers, *J. Electrochem. Soc.* **119**, 1332 (1972).

²⁹⁶ L. Ya. Kheifets and N. P. Demchenko, *Monokrist. Stsintill. Org. Lyuminofovy*, 122 (1969); *Chem. Abstr.* **76**, 14405 (1972).

²⁹⁷ A. Albert, R. J. Goldacre, and J. N. Phillips, *J. Chem. Soc.*, 2240 (1948).

²⁹⁸ G. B. Barlin, *J. Chem. Soc. B*, 641 (1967).

²⁹⁹ For isoxazole a pK_a value of +1.3 reported previously by G. Speroni and P. Pino, *Gazz. Chim. Ital.* **80**, 549 (1950), has been doubted by Haake and Bausher,³⁰⁰ and indeed a reexamination²⁴⁰ has given the value reported above in the text.

TABLE IX

BASIC AND ACID pK VALUES OF OXAZOLE CARBOXYLIC ACIDS^{a, b}

Substituent	pK_a (basic)	pK_a (acidic)
2-COOH-5-Ph	-1.87	1.78
2-COOH-5- <i>p</i> -Cl.C ₆ H ₄	-1.81	1.68
2-COOH-5- <i>p</i> -O ₂ N.C ₆ H ₄	—	1.54
4-COOH	—	3.41
4-COOH-2-Ph	—	3.41
4-COOH-2-Me	-0.66	3.54
4-COOH-2, 5-Me ₂	0.27	4.12
4-COOH-2, 5-Ph ₂	-1.32	3.35
5-COOH-4-Me ^c	-0.72	2.83
5-COOH-2, 4-Me ₂	0.38	3.03
5-COOH-2, 4-Ph ₂	-1.44	2.4

^a From Brown and Ghosh.²⁴⁰^b Measured in aqueous media at 20° spectrometrically.^c Haake and Bausher³⁰⁰ have reported the pK_a values of this compound as +0.95 and 2.88, obtained by potentiometric titration. The first pK_a is probably in error.

The same trend in basicity has been observed by Haake and Bausher^{279, 300} among 4-methyl-1,3-heteroazoles. Thus, 4-methyloxazole (pK_a 1.07) is about 100 times less basic than 4-methylthiazole (3.07), and about 10⁶ times less basic than 4-methylimidazole (7.61).³⁰¹

Substituent effects on the basicity and acidity of oxazoles have been discussed by Brown and Ghosh.²⁴⁰ The effects of 5-substitution on the basic strengths of 4-methyl- and 2,4-dimethyloxazole are summarized in the closely rectilinear plots of Hammett substituent constants (σ_m) versus pK_a values in Fig. 2. From the data in the Tables VIII and IX, and also from Fig. 2, it is evident that the introduction of a 2-methyl group increases the pK_a of an oxazole by an abnormally high increment (~ 1.6 units), whereas a 4-methyl group (also adjacent to the site of protonation) produces a much smaller increase (~ 0.6), comparable to that from a 5-methyl group. Oxazoles bearing an electron-withdrawing

^{299a} L. R. Snyder and B. E. Buell, *J. Chem. Eng. Data* **11**, 545 (1966).³⁰⁰ P. Haake and L. P. Bausher, *J. Phys. Chem.* **72**, 2213 (1968).³⁰¹ F. Schneider, *Z. Physiol. Chem.* **338**, 131 (1964); *Chem. Abstr.* **62**, 11905 (1965).

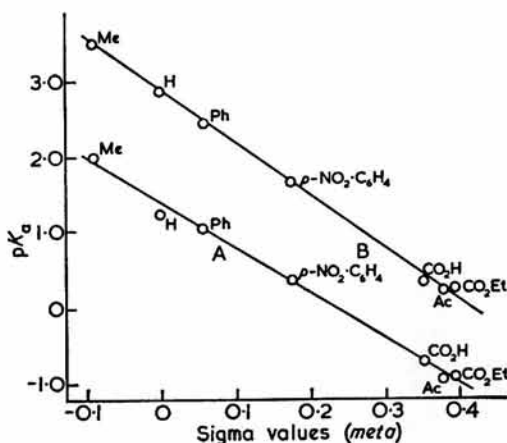


FIG. 2. Plots of pK_a values for 4-methyl-(A) and 2,4-dimethyl-5-substituted oxazoles (B) against the Hammett (*meta*)- σ constants. [Reproduced with permission from D. J. Brown and P. B. Ghosh, *J. Chem. Soc. B*, 270 (1969).]

substituent at C-4 (such as Ac, COOEt, COOH) have pK_a values very similar to those of the respective 5-isomers, a fact readily explained in terms of stabilization of the cation by hydrogen-bonding with the carbonyl group of the 4-substituent. However, with 4- and 5-*p*-nitrophenyloxazole, in both of which such bonding is impossible, the 4-isomer is the weaker base.²⁴⁰

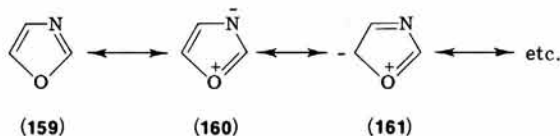
The acidic pK_a values of the carboxyoxazoles (see Table IX) furnish a direct guide to the electron distribution over the three carbon atoms. The acidic strength of the isomers is clearly in the order $2 > 5 > 4$, the reverse of that expected if the acid-weakening effect of the hydrogen bonding between each acid group and the adjacent O and/or N atoms were the determining factor.²⁴⁰

The acidity of H-2 in oxazoles and oxazolium salts, and their comparative rates of deuteration, have been discussed before (see Section III,G). The rates for 2-deuteration of 4- and/or 5-substituted oxazoles in $\text{CH}_3\text{ONa}-\text{CH}_3\text{OD}$ (at $H_L \sim 14.4$) have been measured by Brown and Ghosh.²⁴⁰ Under strongly alkaline conditions oxazole undergoes instantaneous 2-deuteration and a slower 5-deuteration, which indicate that the electron density at the three C atoms of oxazole is in the order $4 > 5 > 2$, a result in agreement with the pK_a values of the three monocarboxyoxazoles. The effect of substituents on the 2-deuteration of oxazoles was consistent with the electronic nature of the groups.

IV. Chemical Properties

A. AROMATIC CHARACTER AND REACTIVITY

The classical structure of oxazole (159) is partly inconsistent with its aromatic character and small dipole moment, but a set of resonance structures involving dipolar forms such as 160 and 161 as contributors



appears to give a more accurate picture. Apparently, the contribution of ionic resonance structures in oxazole is more important than that in benzene. For this reason, the oxazole ring possesses greater reactivity, or in other words, less stability towards electrophilic and nucleophilic reagents. There seems to be only one reported instance of reaction of a free radical with an oxazole.³⁰²

In their resistance towards ring scission by acids, the oxazoles are considered to be somewhat more stable than the furans but less stable than the pyridines. This stability of oxazoles is also reflected in their formation under strongly acidic conditions. The ring is also remarkably stable to alkali but may be opened by nucleophilic reagents such as ammonia, 2,4-dinitrophenylhydrazine, and malononitrile and base under certain conditions.

The oxazole ring is relatively easily cleaved by many oxidizing agents such as permanganate,^{37,303} chromic acid,^{303,304} or hydrogen peroxide.³⁰⁴ The oxidation products are often the acids, amides, or imides (RCONH-COCOR) containing the substituent present in oxazole. A comprehensive bibliography of the action of oxidizing agents on oxazoles and the resulting products has been given by Cornforth⁴ in an earlier review. Oxidation of 4,5-diaryloxazoles with chlorine or bromine leads to the corresponding benzils in high yields.^{304,305} The stability of oxazoles to reduction varies considerably, depending on the type of reducing agents. Both chemical

³⁰² J. W. Cornforth and E. Cookson, *J. Chem. Soc.*, 1085 (1952).

³⁰³ M. Ionescu and C. Makkay, *Stud. Univ. Babes-Bolyai, Ser. Chem.* **16**, 61 (1971); *Chem. Abstr.* **76**, 126841 (1972).

³⁰⁴ T. van Es and O. G. Backeberg, *J. Chem. Soc.*, 1363 (1963).

³⁰⁵ T. van Es and O. G. Backeberg, *J. Chem. Soc.*, 1371 (1963).

and catalytic reductions often lead to ring-opening and give a variety of products; these are discussed later (see Section IV, F).

Considerable advances have been made in recent years in the understanding of the aromatic substitution reactions of oxazoles. Molecular orbital calculations (Section III, B) predict that electrophilic attack should occur preferentially at position 5, and indeed this is observed. The relative order of reactivity calculated theoretically is not in complete accord with the experimentally observed order ($5 > 4 > 2$); therefore it is evident that the electrophilic substitution reactions are rather more complex than the present theoretical calculations would predict.

The oxazoles also display a number of characteristics that are typical of the furans and are explained by the structural similarity of these heterocyclic systems. The ease with which they undergo Diels-Alder reactions with dienophiles and autooxidation with singlet oxygen (see Sections IV, D and E) clearly demonstrates that oxazoles are not fully aromatic. This fact and ultraviolet data (Section III, E) suggest that oxazoles should be considered partly as conjugated dienes.

The autoassociation phenomena of oxazole and 2,4-dimethyloxazole have been studied by Meyer *et al.*³⁰⁶ A cryometric analysis of the inert solvent-oxazole binary system reveals the existence of intermolecular oxazole-oxazole type association. Data obtained with 2,4-dimethyloxazole indicate the importance of steric hindrance in this type of association.³⁰⁶ Oxazoles readily form stable complexes with metal salts of the general formula BMX_2 (where M is a bivalent metal cation).^{195,196} These are very useful in isolation and characterization of oxazoles.

B. ELECTROPHILIC SUBSTITUTION REACTIONS

1. Halogenation

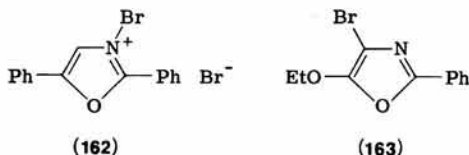
The halogenation of a number of substituted oxazoles has been studied by Gompper and Rühle.^{307,308} They found that the nuclear bromination of oxazoles either with bromine or with *N*-bromosuccinimide occurs preferentially at C-5; if this was occupied, then at C-4, but not at C-2. Similar observations were later reported in brominations with liquid

³⁰⁶ M. Meyer, R. Meyer, and J. Metzger, *J. Chim. Phys. Physicochim. Biol.* **67**, 1380 (1970).

³⁰⁷ R. Gompper and H. Rühle, *Liebigs Ann. Chem.* **626**, 83 (1959).

³⁰⁸ R. Gompper and H. Rühle, *Liebigs Ann. Chem.* **626**, 92 (1959).

bromine in carbon tetrachloride or glacial acetic acid.^{18, 115, 284, 285, 309-311} In some instances, for example with 2,5-diphenyloxazole, only the oxazole-bromine adducts (**162**) are obtained.³⁰⁷ Electrophilic substitution in the phenyl groups of 4,5-diphenyloxazoles by bromine could not be effected even in the presence of catalysts such as iron filings, iodine, or ferric chloride.³⁰⁴



Bromination of 2-phenyl-5-ethoxyoxazole with *N*-bromoacetamide gives 2-phenyl-4-bromo-5-ethoxyoxazole (**163**), an unstable liquid which does not form a Grignard reagent.²

N-Bromophthalimide and dioxane dibromide have been found less effective for bromination;³⁰⁷ oxidation reactions predominate. Chlorination of 2-methyl-4,5-diphenyloxazole in chloroform at room temperature after 14 days results in the formation of 4,5-dichloro-2-trichloromethyl-4,5-diphenyl-2-oxazoline, which is basically an addition compound.³⁰⁷

2. Mercuration

The behavior of oxazoles towards mercuric acetate, which results in formation of electrophilically substituted products, has been studied by Shvaika and Klimisha.^{312, 313} Mercuration of phenyloxazoles in acetic acid results in products mercurated only at the unsubstituted C atoms in the heterocyclic ring. Like halogenation, the order of reactivity of the various positions in the ring is C-5 > C-4 > C-2. The hydrolysis of the mercurated oxazoles with dioxane-concentrated hydrochloric acid regenerates the parent oxazoles,³¹³ whereas treatment with halogens (bromine or iodine) gives the corresponding halo-oxazole in 55-90% yields.^{18, 312} The reaction thus offers an indirect but efficient method of introduction of

³⁰⁹ T. Saito, Japanese Patent 20538 (1967); *Chem. Abstr.* **69**, 10427 (1968).

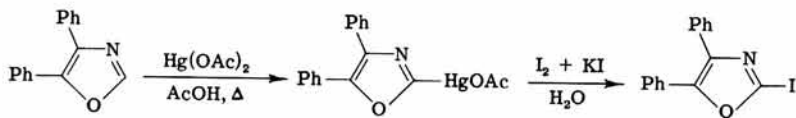
³¹⁰ N. Saito, T. Kurihara, K. Yamanaka, S. Tsuruta, and S. Yasuda, *Yakugaku Zasshi* **88**, 1289 (1968); *Chem. Abstr.* **70**, 37686 (1969).

³¹¹ I. Simiti and E. Chindris, *Arch. Pharm. (Weinheim)* **305**, 509 (1972).

³¹² O. P. Shvaika and G. P. Klimisha, *Dopov. Akad. Nauk Ukr. RSR*, 1479 (1965); *Chem. Abstr.* **65**, 7159 (1966).

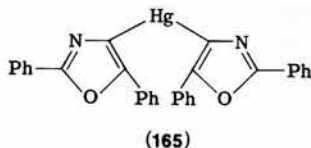
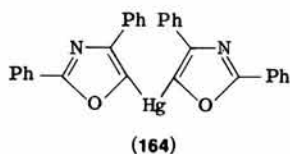
³¹³ O. P. Shvaika and G. P. Klimisha, *Khim. Geterotsikl. Soedin.* **2**, 19 (1966); *Chem. Heterocycl. Compounds* **2**, 14 (1966).

halogens into the oxazole ring through electrophilic substitution (Scheme 8).



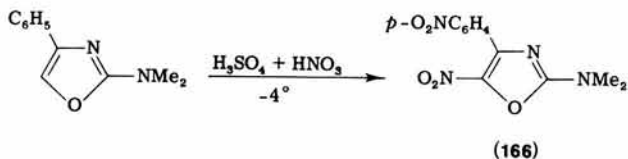
Scheme 8

Symmetrical bis(oxazolyl)mercury derivatives (**164** and **165**) are obtained by treatment of the appropriate oxazolylmercury acetates with sodium stannite.^{312, 313}



3. Nitration, Sulfonation, and Chlorosulfonation

The only recorded instance of a nitration of an oxazole derivative where the nitro group substitutes a ring hydrogen is the formation, in 97% yield, of 5-nitro-2-dimethylamino-4-(*p*-nitrophenyl)oxazole (**166**) from



2-dimethylamino-4-phenyloxazole by nitration with a mixture of concentrated sulfuric and nitric acids at -4°C .¹⁰⁴ In general, however, both nitration^{39, 161} and sulfonation^{19, 314} of substituted oxazoles occur only in the phenyl groups, and occupy almost invariably the para-position.³⁰⁴ Thus, on nitration 2-methyl-4,5-diphenyloxazole forms the corresponding di-*p*-nitrophenyl derivative, whereas sulfonation attacks only the 5-phenyl group. 2,4,5-Triphenyloxazole can be converted to the tris(*p*-nitrophenyl) derivative.³⁰⁴ Chlorosulfonation with chlorosulfuric acid analogously takes place at the para-position of the phenyl ring.³⁰⁴

The relative reactivities of the phenyl groups in the 2-, 4-, and 5-positions of oxazole towards electrophilic attack are in the order C-5 > C-4 > C-2.

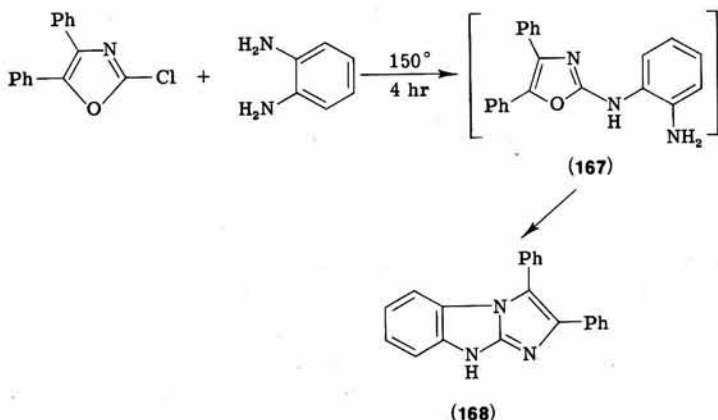
³¹⁴ O. Trösken, German Patent 869,490 (1953); *Chem. Abstr.* **52**, 16372 (1958).

Recently Simiti and Chindris³¹¹ have reported that on nitration of 2-(*p*-substituted)phenyl-4-chloromethyloxazoles, the nitro group was always introduced in the position ortho to the existing substituent on phenyl.

C. NUCLEOPHILIC ATTACK

Halogen substituents in the 2-position are reactive and are relatively easily replaceable by aminoalkyl,¹⁰⁶ hydrazino,³¹⁷ alkoxy, and hydroxy groups.^{315, 316} The order of the mobility of ring halogens toward nucleophiles is $X-2 \gg X-4 > X-5$.³⁰⁸

The reaction of 4,5-disubstituted 2(3*H*)-oxazolones with phosphorus oxychloride leads to the formation of the corresponding 2-chlorooxazoles.^{315, 316} 2-Chlorooxazoles on heating with formamide or acetamide at a high temperature for 3–4 hours and then pouring into water yield the corresponding 2(3*H*)-oxazolones (2-hydroxyoxazoles).³¹⁶ Nucleophiles derived from active methylene compounds also displace the 2-chloro substituent. A multifunctional nucleophile may bring about secondary reactions also. For example, 4,5-diphenyl-2-chlorooxazole on heating at 150° with *o*-phenylenediamine forms 1,2-diphenylimidazo[1,2-*a*] benzimidazole (168)³¹⁶ supposedly through the normal displacement product 167.



Metalation of 2-unsubstituted oxazoles with *n*-butyllithium at low temperature produces the corresponding 2-lithio derivatives, which are useful intermediates for the preparation of deuterium-labeled com-

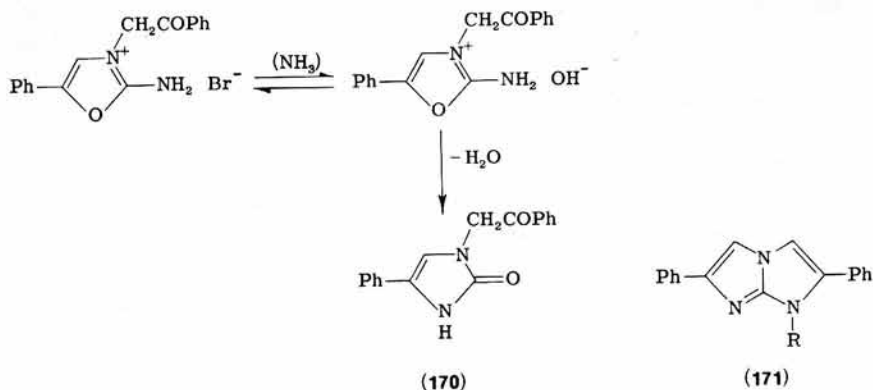
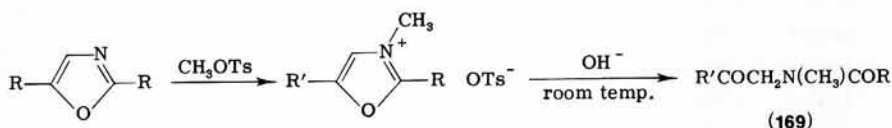
³¹⁵ R. Gompper and F. Effenberger, *Angew. Chem.* **70**, 628 (1958).

³¹⁶ R. Gompper and F. Effenberger, *Chem. Ber.* **92**, 1928 (1959).

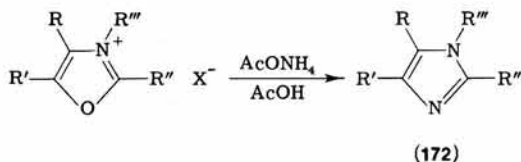
³¹⁷ H. Beyer, S. Melde, and K. Dittrich, *Z. Chem.* **1**, 191 (1961).

pounds.^{284, 285} 4- and 5-Lithio derivatives of oxazoles are obtainable by metal-halogen exchange reaction of the respective bromooxazoles and *n*-butyllithium in ether at low temperatures.^{284, 285, 318}

Quaternized oxazoles are readily attacked by hydroxide, ammonia, and amines. Cleavage of the oxazole ring is observed by attack of hydroxide, undoubtedly at position 2, and *N*-methyl- α -acylamino ketone (169) is formed.³¹⁹ Treatment of 2-amino-5-phenyl-3-phenacyloxazolium bromide with ammonia gives 4-phenyl-1-phenacyl-2-imidazolone (170) by ring-opening and reclosure. A similar reaction with aliphatic amines (RNH₂) leads to 1-substituted 2,6-diphenylimidazo[1,2-*a*]imidazoles (171).³²⁰



2,3,4,5-Tetrasubstituted oxazolium perchlorates or methyl sulfates on heating with ammonium acetate in acetic acid are readily converted into the corresponding tetrasubstituted imidazoles (172) in good yields.³²¹



³¹⁸ R. Lakhan, unpublished work (1971).

³¹⁹ D. G. Ott, F. N. Hayes, and V. N. Kerr, *J. Amer. Chem. Soc.* **78**, 1941 (1956).

³²⁰ A. Hetzheim and H. Pusch, *Z. Chem.* **10**, 385 (1970).

³²¹ R. Gompper, *Chem. Ber.* **90**, 374 (1957).

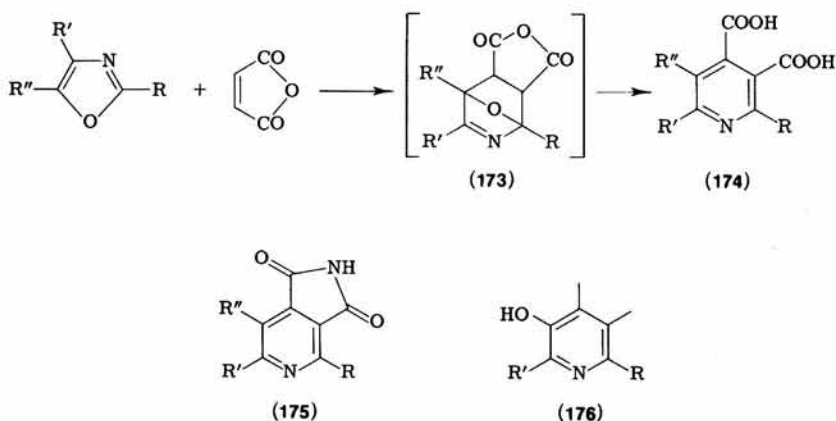
Treatment of 2,3,5-trisubstituted oxazolium perchlorates with gaseous ammonia in ethanol leads to 2-hydroxy- Δ^3 -imidazoline derivatives, while the corresponding imidazolinium perchlorates form when aromatic primary amines are used.³²²

D. REACTIONS AS CONJUGATED AZADIENES

Reactions of oxazoles indicate that they are not fully aromatic substances and that the azadiene system present readily reacts with dienophiles by the Diels-Alder mechanism. The bicyclic adducts formed in these condensations undergo facile aromatization, particularly in acid media, by elimination of a molecule of water, an alcohol, hydrocyanic acid, a nitrile, or hydrogen, forming substituted pyridine bases. The course of the reaction is highly dependent on the substituents on the oxazole ring, the nature of the dienophile, and the reaction conditions.

The reaction has been very useful for the synthesis of substituted pyridines, particularly pyridoxine (vitamin B₆) and its homologs and analogs. In the last decade a number of papers and patents dealing with the interaction of oxazoles with dienophiles, leading to pyridines, have appeared, they were critically reviewed by Karpeiskii and Florent'ev¹¹ in 1969. Therefore, reactions leading to pyridines are described here only briefly, in order to give a clear picture of the scope of the reaction.

In the late 1950s Kondrat'eva^{323, 324} first showed that alkyloxazoles



³²² G. M. Dorofeenko, L. V. Mezheritskaya, and V. I. Dulenko, *Khim. Geterotsikl. Soedin.*, Sb. 2: *Kislordsoderzhashchie Geterotsikly*, 287 (1970); *Chem. Abstr.* **76**, 140618 (1972).

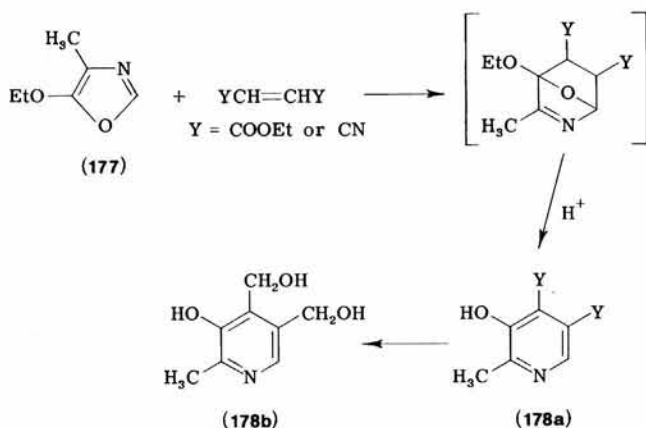
³²³ G. Ya. Kondrat'eva, *Khim. Nauka Prom.* **2**, 666 (1957); *Chem. Abstr.* **52**, 6345 (1958).

³²⁴ G. Ya. Kondrat'eva, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 484 (1959); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 457 (1959).

undergo Diels-Alder reaction with maleic anhydride in benzene to give substituted cinchomeronic acids (**174**) in good yields, presumably by cleavage of the oxygen-bridge of the initially formed adduct **173**. Reaction with maleimide in the presence of hydroquinone³²⁵ or with fumaronitrile in the presence of a trace of picric acid³²⁶ gives the corresponding pyridine-3,4-dicarboximide (**175**) or 3,4-dicyanopyridine derivative. Analogously, 5-alkoxyoxazoles give the corresponding 3-hydroxypyridines (**176**).^{325, 327}

A study of the effect of substituents on the reactivity of oxazoles^{328, 329} under Diels-Alder conditions has shown that reactivities follow the order: alkoxy > alkyl ~ 4-phenyl > acetyl > ethoxycarbonyl >> 2- and 5-phenyl. The failure of the 2- and 5-phenyl-substituted oxazoles to react as heterodienes is partly due to the increase in steric crowding and partly arises from the deconjugation of the phenyl rings which would occur during the intermediate adduct formation, in comparison with analogous alkyl derivatives. Lengthening of the carbon chain in the 2-position of the oxazole ring reduces the activity of the diene system, as is shown by the drop in yield of the product from 54% to 40% on going from methyl to *n*-amyl.³²⁷

A short synthesis of pyridoxine (**178b**) utilizing the Diels-Alder reaction



³²⁵ G. Ya. Kondrat'eva and C.-H. Huang, *Dokl. Akad. Nauk SSSR* **141**, 628 (1961); *Proc. Acad. Sci. USSR, Chem. Sect.* **141**, 1169 (1961).

³²⁶ V. A. Puchnova and E. A. Luk'yanets, *Khim. Geterotsikl. Soedin.*, Sb. 2: *Kislород-soderzhashchie Geterotsikly*, 327 (1970); *Chem. Abstr.* **76**, 140453 (1972).

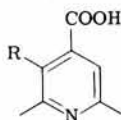
³²⁷ G. Ya. Kondrat'eva and C.-H. Huang, *Dokl. Akad. Nauk SSSR* **141**, 861 (1961); *Proc. Acad. Sci. USSR, Chem. Sect.* **141**, 1221 (1961).

³²⁸ C.-H. Huang and G. Ya. Kondrat'eva, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 525 (1962).

³²⁹ G. Ya. Kondrat'eva and C.-H. Huang, *Dokl. Akad. Nauk SSSR* **142**, 593 (1962); *Proc. Acad. Sci. USSR, Chem. Sect.* **142**, 59 (1962).

of 4-methyl-5-ethoxyoxazole (177) to construct the pyridine ring, was first achieved by Harris and his co-workers⁶⁵ in 1962. Later research has shown that 5-alkoxy-,^{68, 69, 73, 330-333} 5-cyano-,^{330, 334} or 5-ethoxycarbonyloxy⁷⁷-substituted 4-methyloxazoles condense with appropriate dienophiles (having a functionality readily convertible into two $-\text{CH}_2\text{OH}$ groups) to give, after acid treatment, 2-methyl-3-hydroxy-4,5-disubstituted pyridines (178a), which eventually have been transformed into vitamin B₆ (178b). A number of analogs of pyridoxine have also been obtained by this method.^{70, 335, 336}

The interaction of oxazoles with unsymmetrical dienophiles yields, as a rule, only one of the two possible isomers, in contrast to the usual Diels-Alder reactions where both possible products are generally obtained.^{337, 337a} Thus, the reaction of 5-alkyl- or 5-alkoxy-substituted oxazoles with acrylic acid leads almost exclusively to the substituted isonicotinic acids (179)



(179)

regardless of the nature of substituents.³³⁷ Similar condensation of 4-methyloxazole with acrylonitrile in toluene, however, gives only 5% of the expected 2-methylisonicotinonitrile, while 12% of 2-methyl-3-pyridinol is obtained.³³⁸ Reaction in a polar solvent (glacial acetic acid) has been

³³⁰ W. Kimel and W. Leimgruber, French Patent 1,384,099 (1965); *Chem. Abstr.* **63**, 4263 (1965).

³³¹ F. Hoffmann-La Roche & Co., A.-G., Netherlands Appl. 6,506,703 (1965); *Chem. Abstr.* **64**, 15851 (1966).

³³² T. Naito, K. Ueno, T. Miki, and H. Omura, Japanese Patent 36,301 (1970); *Chem. Abstr.* **74**, 64211 (1971).

³³³ T. Naito, Y. Morita, K. Ueno, S. Shimada, S. Miyazaki, and T. Fujiwara, Japanese Patent 39,259 (1970); *Chem. Abstr.* **74**, 125462 (1971).

³³⁴ F. Hoffmann-La Roche & Co., A.-G., Netherlands Appl. 6,404,750 (1964); *Chem. Abstr.* **62**, 11818 (1965).

³³⁵ V. L. Florentiev, N. A. Drobinskaya, L. V. Ionova, and M. Ya. Karpeisky, *Tetrahedron Lett.*, 1747 (1967).

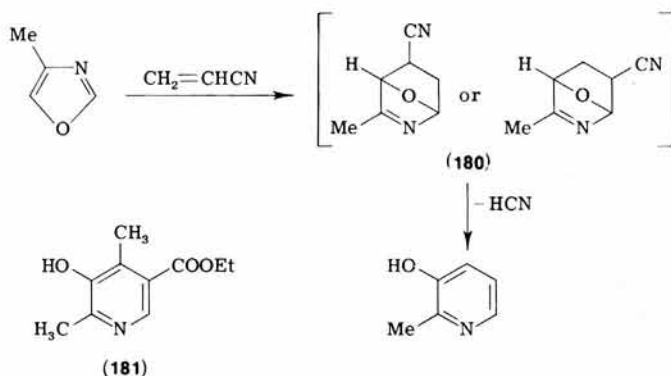
³³⁶ N. D. Doktorova, L. V. Ionova, M. Ya. Karpeisky, N. Sh. Padyukova, K. F. Turchin, and V. L. Florentiev, *Tetrahedron* **25**, 3527 (1969).

³³⁷ G. Ya. Kondrat'eva and C.-H. Huang, *Dokl. Akad. Nauk SSSR* **164**, 816 (1965); *Proc. Acad. Sci. USSR, Dokl. Chem.* **164**, 939 (1965).

^{337a} G. Ya. Kondrat'eva, L. B. Medvedskaya, and Z. N. Ivanova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2125 (1972).

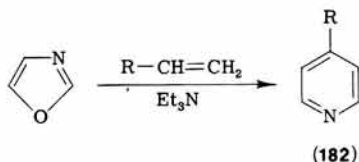
³³⁸ T. Naito, T. Yoshikawa, F. Ishikawa, S. Isoda, Y. Omura, and I. Takamura, *Chem. Pharm. Bull.* **13**, 869 (1965).

shown to give only the 3-pyridinol derivative in 28% yield. The reaction is quite general with 5-unsubstituted oxazoles, and the formation of 3-pyridinols is explained by the aromatization of the adduct (e.g., **180**) by



the cleavage of the oxygen-bridge and elimination of hydrogen cyanide.³³⁹ Analogously, a 3-pyridinol derivative (**181**) is obtained by the condensation of ethyl crotonate with 4-methyloxazole.³³⁹

Oxazole itself, in contrast to isoxazole, thiazole, and imidazole has been found to undergo Diels-Alder reaction with dienophiles.^{340, 341} Isonicotinic acid esters (**182**, $\text{R} = \text{COOR}'$) and isonicotinitriles (**182**, $\text{R} = \text{CN}$) are



obtained by the reaction of oxazole with acrylic esters or acrylonitrile in the presence of triethylamine.³⁴¹

Extensive studies on the mechanism^{342, 343} of the Diels-Alder reaction of oxazoles have clearly demonstrated that the formation of pyridine bases fundamentally involves two (or possibly three) steps: the condensation of oxazoles with dienophiles giving the bicyclic adducts (**183**), and

³³⁹ T. Yoshikawa, F. Ishikawa, and T. Naito, *Chem. Pharm. Bull.* **13**, 878 (1965).

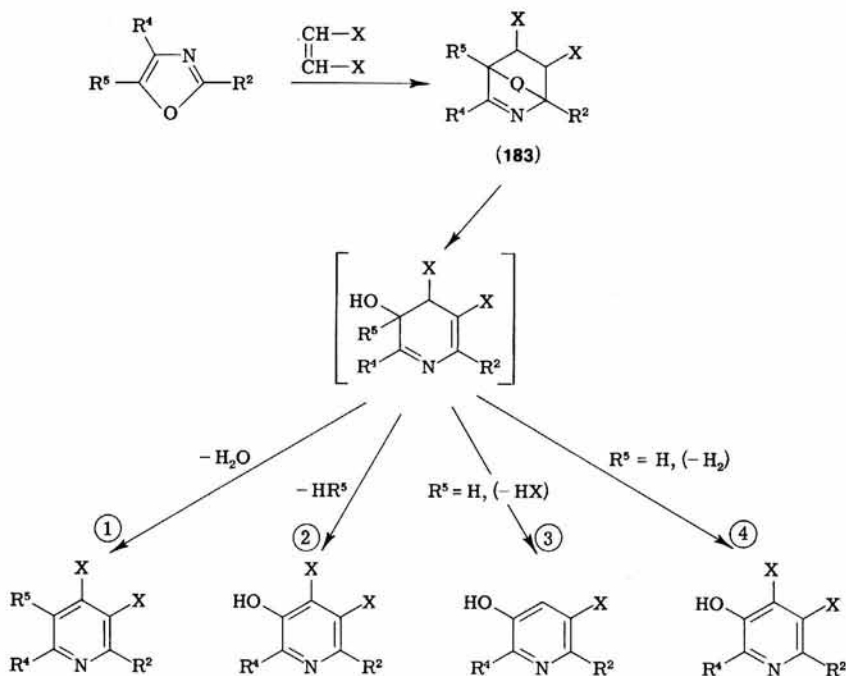
³⁴⁰ I. I. Grandberg and A. N. Kost, *Zh. Obshch. Khim.* **29**, 1099 (1959); *J. Gen. Chem. USSR* **29**, 1060 (1959).

³⁴¹ P. Colin, French Patent, 1,550,352 (1968); *Chem. Abstr.* **72**, 31629 (1970).

³⁴² T. Yoshikawa, F. Ishikawa, Y. Omura, and T. Naito, *Chem. Pharm. Bull.* **13**, 873 (1965).

³⁴³ T. Naito and T. Yoshikawa, *Chem. Pharm. Bull.* **14**, 918 (1966).

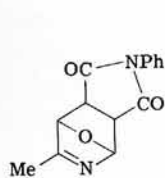
subsequent aromatization of these by cleavage of the oxygen-bridge with simultaneous or stepwise elimination of the two substituents attached to C-3 and C-4 of **183**. The last step, depending largely on the structure



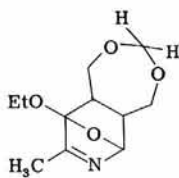
Scheme 9

of the starting compounds, is supposed to occur in four principal ways (Scheme 9). Generally the synthesis proceeds by more than one pathway, simultaneously yielding a heterogeneous mixture of products. Of the four types shown in Scheme 9, the last reaction pathway involving the removal of a hydride ion either from the 3- or 4-position is energetically less favorable, and therefore rare. However, the presence of a hydride ion acceptor such as hydrogen peroxide has been shown to catalyze the reaction and give a better yield of the pyridine.³⁴²

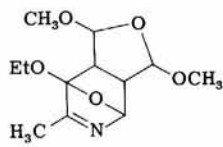
The bicyclic adducts of the type **183** are extremely unstable, but in certain cases they have been isolated and rigorously characterized. Typically, the condensation of 4-methyloxazole with *N*-phenylmaleimide yields the adduct **184**,³⁴³ the stereochemistry of which has not been studied. The adducts **185** and **186**, obtained by the condensation of 5-ethoxy-4-



(184)



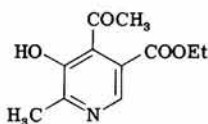
(185)



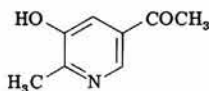
(186)

methyloxazole with 4,7-dihydro-1,3-dioxepin³³¹ and *cis*- and *trans*-2,5-dimethoxy-2,5-dihydrofuran,³⁴⁴ respectively, have been separated into the endo and exo racemates.

Attempts have also been made^{336,345} to find a theoretical explanation of the stereo or positional selectivity in the first stage of the heterodiene synthesis, especially in the interaction between 5-ethoxy-4-methyloxazole and asymmetric dienophiles, e.g., β -acetylacrylic acid and its ethyl ester. π -Electron density calculations for the diene and dienophile molecules by the HMO method indicate the formation of the 4-acetylpyridine derivative (187) from ethyl β -acetylacrylate, while the opposite orientation would be expected in the reaction with the free acid, giving a substituted 5-acetylpyridine as the main product. Indeed, 5-ethoxy-4-methyloxazole on condensation with ethyl β -acetylacrylate affords only 187, while in the condensation with β -acetylacrylic acid, only 2-methyl-3-hydroxy-5-acetylpyridine (188) is isolated.^{336,345}



(187)



(188)

The condensation of ethyl 5-ethoxyoxazole-4-acetate (189) with a variety of dienophiles has permitted the syntheses of several 4,5-disubstituted 2-ethoxycarbonylmethyl-3-pyridinols.^{346,347} Very often the

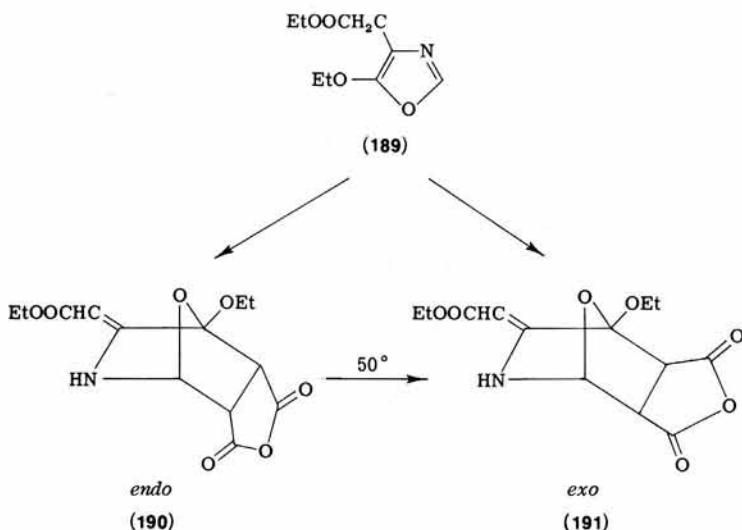
³⁴⁴ T. Naito, K. Ueno, M. Sano, Y. Omura, I. Itoh, and F. Ishikawa, *Tetrahedron Lett.*, 5767 (1968).

³⁴⁵ N. A. Drobinskaya, L. V. Ionova, M. Ya. Karpeiskii, N. Sh. Padyukova, K. F. Turchin, and V. L. Florent'ev, *Khim. Geterotsikl. Soedin.* **6**, 37 (1970); *Chem. Heterocycl. Compounds* **6**, 33 (1970).

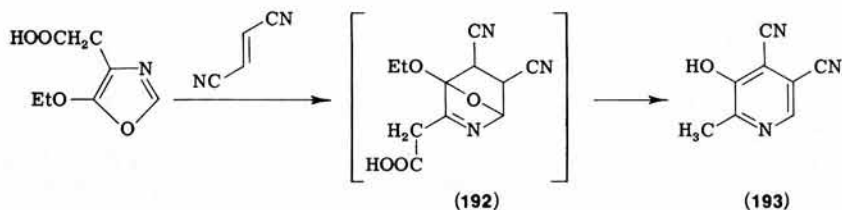
³⁴⁶ T. Miki and T. Matsuo, *J. Pharm. Soc. Jap.* **87**, 323 (1967).

³⁴⁷ M. Kawazu, K. Azuma, and M. Wada, Japanese Patent 26,492 (1970); *Chem. Abstr.* **74**, 53544 (1971).

intermediate bicyclic adducts, having an exocyclic bond, have been isolated as crystalline solids in high yields.^{336,348} As an illustrative example, condensation of **189** with maleic anhydride gives the *endo* (**190**) and *exo* (**191**) adducts; the former easily isomerizes to the latter on heating.³⁴⁸



On the other hand, the bicyclic intermediates (e.g., **192**) have never been isolated from the reaction of 5-ethoxyoxazole-4-acetic acid³⁴⁹ with the dienophiles; rather the decarboxylated compounds (e.g., **193**) are invariably obtained as the end products, presumably through **192**.³⁵⁰ Matsuo and Miki³⁵⁰ have also shown that the reaction with asymmetric dienophiles occurs to introduce an electron-attracting group preferentially at the 4-position of the pyridine nucleus.

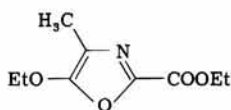


³⁴⁸ T. Matsuo and T. Miki, *Chem. Pharm. Bull.* **20**, 669 (1972).

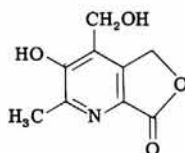
³⁴⁹ T. Miki and T. Matsuo, Japanese Patent 16,502 (1971); *Chem. Abstr.* **75**, 36002 (1971).

³⁵⁰ T. Matsuo and T. Miki, *Chem. Pharm. Bull.* **20**, 806 (1972).

The condensation of ethyl 4-methyl-5-ethoxyoxazole-2-carboxylate (194) with 2-isopropyl-4,7-dihydro-1,3-dioxepin on refluxing gives a 66% yield of 4-methyl-5-hydroxy-6-(hydroxymethyl)-2-oxodihydrofuro[3,4-*b*]-pyridine (195).³⁵¹

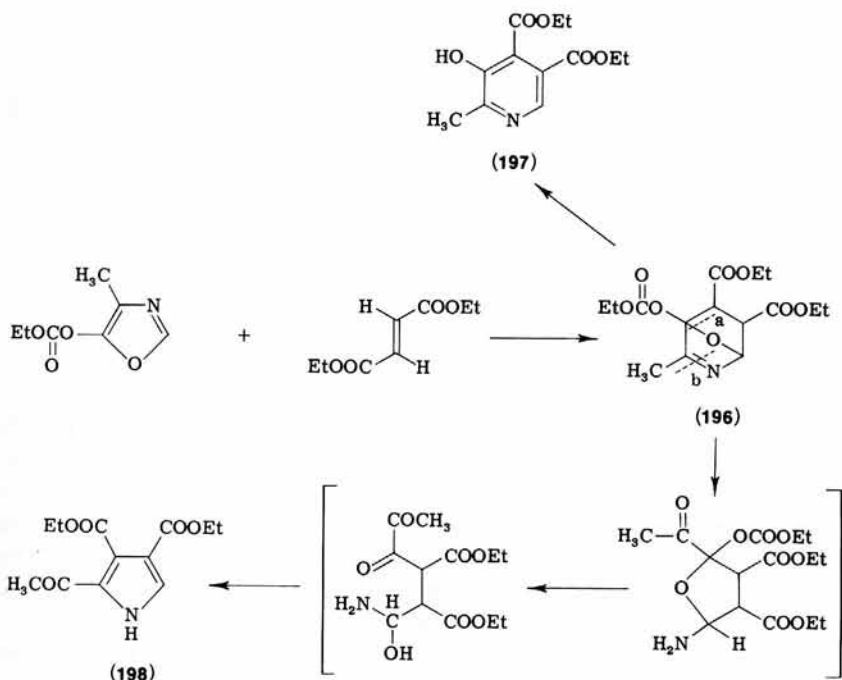


(194)



(195)

Murakami *et al.*³⁵² made an interesting observation in a study of the reaction of 5-ethoxycarbonyloxy-4-methyloxazole with diethyl fumarate.



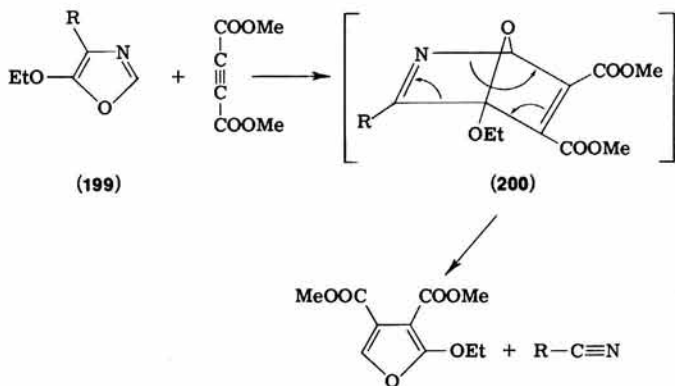
Scheme 10

³⁵¹ M. Takehara, K. Togo, Y. Maeda and Y. Yoshida, Japanese Patent 07,553 (1972); *Chem. Abstr.* 77, 114447 (1972).

³⁵² M. Murakami, K. Takahashi, J. Matsumoto, K. Tamazawa, K. Murase, H. Iwamoto, and M. Iwanami, *Bull. Chem. Soc. Jap.* 41, 628 (1968).

It was noted that the decomposition of the addition product (196) may proceed simultaneously by two different routes, giving either the expected pyridine derivative (197) or pyrrole derivative (198) as the major product (Scheme 10). Treatment with ethanolic hydrochloric acid gives mainly 197 (formed by cleavage of the C—O bond of the adduct), while aqueous hydrochloric acid gives mainly 2-acetyl-3,4-bis(ethoxycarbonyl)pyrrole (198), probably by hydrolysis of the C=N bond of adduct 196. Similar results have been obtained with 4-methyl-5-ethoxyoxazole.³⁵²

The fate of the bicyclic Diels–Alder adducts derived by the interaction of oxazoles with dienophiles containing a triple bond is very different from those considered above. In such cases ready elimination of hydrogen cyanide or a nitrile by the retro-diene cycloaddition mechanism (also called retro-Diels–Alder reaction) is generally observed. Typically, the reaction of 5-ethoxyoxazoles (199) with dimethyl acetylenedicarboxylate



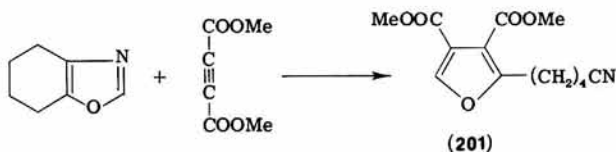
in cold ether leads to dimethyl 2-ethoxyfuran-3,4-dicarboxylate in 51–53% yield, together with the appropriate nitrile.^{353,354} The less reactive substituted oxazoles require refluxing in benzene or toluene and give the expected furan-3,4-dicarboxylic esters in up to 90% yields, and nitriles containing the substituent originally at C-4 of the oxazole.^{353–355} The reaction with 4,5-tetramethyleneoxazole in refluxing ether yields the dimethyl ester of 2-(4-cyanobutyl)furan-3,4-dicarboxylic acid (201).³⁵⁵

4-Monosubstituted oxazoles (or oxazole itself) in this way may offer a route to 3-mono- or 3,4-disubstituted furans by reaction with appropriate

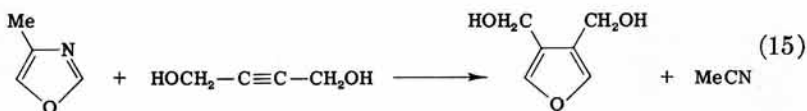
³⁵³ R. Grigg, R. Hayes, and J. L. Jackson, *J. Chem. Soc. D*, 1167 (1969).

³⁵⁴ R. Grigg and J. L. Jackson, *J. Chem. Soc. C*, 552 (1970).

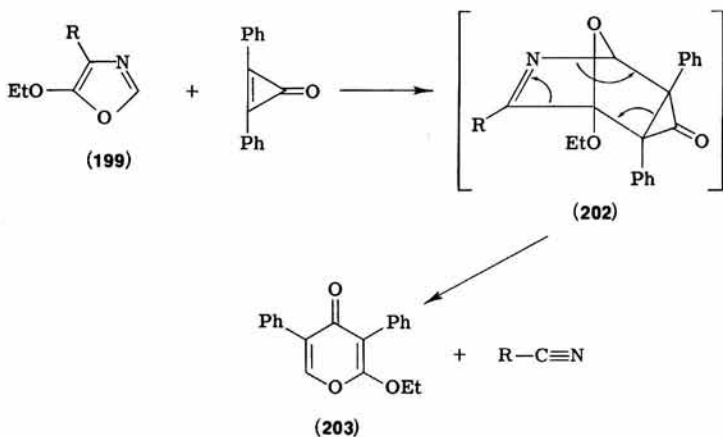
³⁵⁵ G. Ya. Kondrat'eva, L. B. Medvedskaya, and Z. N. Ivanova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2276 (1971); *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **20**, 2148 (1971).



acetylenic dienophiles. Thus, 4-phenyloxazole has been shown to react with propiolic acid and acetylacetylene to give moderate yields of 3-furoic acid and 3-acetylfuran, respectively,³⁵⁶ whereas 4-methyloxazole gives a 67% yield of 3,4-bis(hydroxymethyl)furan on heating with 2-butyne-1,4-diol at 170° for 24 hours under nitrogen³⁵⁷ [Eq. (15)].



Once again, of alkyl-, acetyl-, carbethoxy-, and alkoxyoxazoles, the last have been found to be the most reactive as azadiens towards dienophiles such as propargaldehyde (*ynal*), acetylacetylene (*ynone*), diacetylacetylene (*yndione*), butynediol diacetal, and acetylenic esters.^{358, 359} The reaction



³⁵⁶ S. Turner and S. R. Ohlsen, *J. Chem. Soc. C*, 1632 (1971).

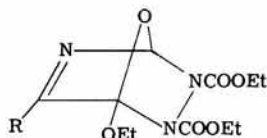
³⁵⁷ F. Graf and H. Koenig, German Offen. 1,935,009 (1971); *Chem. Abstr.* **74**, 64201 (1971).

³⁵⁸ G. Ya. Kondrat'eva, L. B. Medvedskaya, Z. M. Ivanova, and L. V. Shmelev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1363 (1971); *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **20**, 1278 (1971).

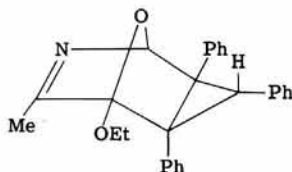
³⁵⁹ G. Ya. Kondrat'eva, L. B. Medvedskaya, Z. M. Ivanova, and L. V. Shmelev, *Dokl. Akad. Nauk SSSR, Ser. Khim.* **200**, 1358 (1971); *Proc. Acad. Sci. USSR, Dokl. Chem.* **200**, 862 (1971).

is particularly useful for the synthesis of the previously unknown class of esters of 2-alkoxyfuran-3-carboxylic acid.

The formation of a γ -pyrone (**203**) from the reaction of 5-ethoxyoxazoles (**199**) with diphenylcyclopropenone constitutes an example of a retro-homo-Diels-Alder reaction.^{353,354} In no case were adducts of the types **200** or **202** isolated. But, nevertheless, stable adducts (**204**, R = H or Me) have been isolated from the oxazoles (**199**, R = H or Me) and diethyl azodicarboxylate in 65–66% yield, whereas **199** (R = Me) gives adduct **205**



(204)



(205)

in 63% yield with triphenylcyclopropene.³⁵⁴ Pyrolysis of adduct **205** gives back the original oxazole (**199**, R = Me) and no acetonitrile.³⁵⁴

E. REACTIONS WITH SINGLET OXYGEN (AUTOXIDATIONS)

Oxazoles are extremely susceptible to the action of singlet molecular oxygen and behave as 1,3-dienes, as they do in the Diels-Alder reaction. The wide variety of reactions observed with singlet oxygen and oxazoles take place, not by diverse modes of attack of the excited oxygen species with the substrate, but rather by a multitude of paths that appear to be open for the decomposition of the intermediate peroxide or hydroperoxide. The secondary decompositions are highly dependent on the structure of the oxazole, the nature of the functional groups in the immediate environment of the newly formed peroxide, the solvent, temperature, and other conditions.

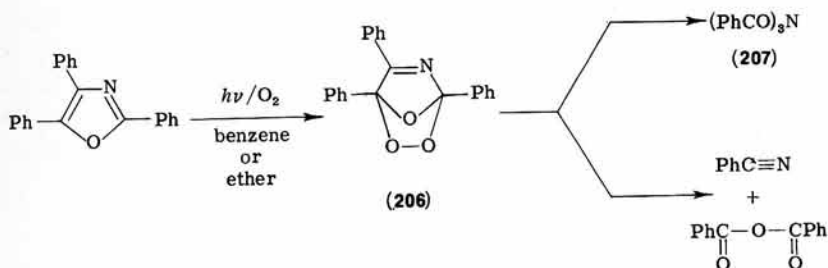
Thus, photooxidation of 2,4,5-triphenyloxazole in ether or benzene in oxygen ($>3000 \text{ \AA}$) yields tribenzoylamide (**207**), benzonitrile, and benzoic anhydride, most probably by rearrangement of the intermediate bicyclic peroxide (**206**) in two different ways.¹⁷⁵

Indeed, the systematic studies by Wasserman *et al.*^{360–362} on the photosensitized autoxidation of oxazoles have shown that this system may be directed to undergo facile destruction of the aromatic ring selectively

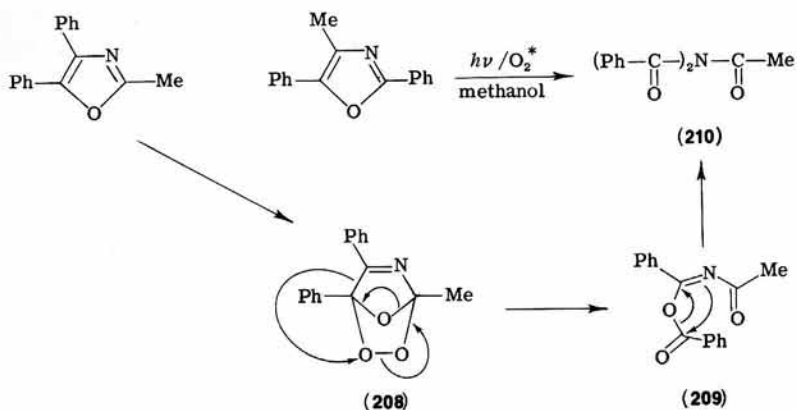
³⁶⁰ H. H. Wasserman and M. B. Floyd, *Tetrahedron Suppl.* **7**, 441 (1966).

³⁶¹ M. B. Floyd, Ph.D. Thesis, Yale University (1966); *Diss. Abstr. B* **27**, 3457 (1967).

³⁶² H. H. Wasserman, *Ann. N.Y. Acad. Sci.* **171**, (Art. 1), 108 (1970).



through either of the above two pathways. Reactions in alcoholic solvents appear to lead to the triacylamine formation exclusively. Thus, both 2-methyl-4,5-diphenyloxazole and 4-methyl-2,5-diphenyloxazole are transformed into *N,N*-dibenzoylacetylamine (210) by air in the presence of visible light in methanol containing methylene blue.^{360,361} The transannular peroxide (208) formed in the first step undergoes a Baeyer-Villiger type of rearrangement with oxygen-insertion leading to isoimide (209), which then undergoes an *O*-acyl to *N*-acyl migration to give the triamide 210. Triphenyloxazole analogously gives *N,N*-dibenzoylbenzamide (207)

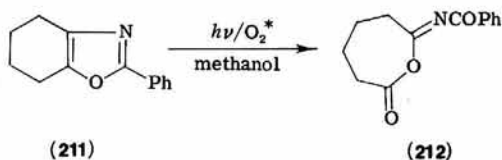


as the main product.³⁶⁰ In cases where the 4-position of the oxazole ring is unsubstituted, photooxidation could lead to triamides containing the *N*-formyl group. This result has recently been observed in the photooxidation of 2,5-diphenyloxazole.^{363,364}

³⁶³ M. E. Ackerman, Ph.D. Thesis, University of New Mexico (1971); *Diss. Abstr. B* 32, 1437 (1971).

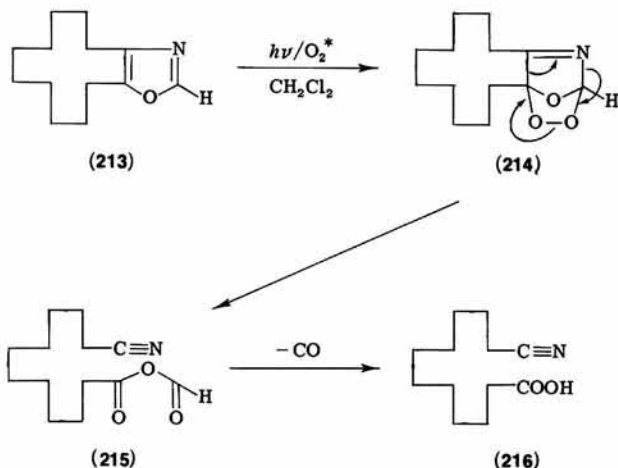
³⁶⁴ M. E. Ackerman, G. H. Daub, F. N. Hayes, and H. A. Mackay, in "Organic Scintillators and Liquid Scintillation Counting" (D. L. Horrocks and C.-T. Peng, eds.), p. 315. Academic Press, New York, 1971.

The highly reactive intermediate isoimides of the type **209** have actually been obtained as reaction products when fused-ring oxazoles are employed as substrates. For example, the photosensitized autoxidation of the phenyl-substituted oxazole **211** in methanol yields the *N*-benzoylimino anhydride (**212**).^{126, 362} Further studies on the reaction of oxazoles with singlet oxygen



to form triamides using ^{18}O -labeling technique have supported the mechanism given.³⁶⁵

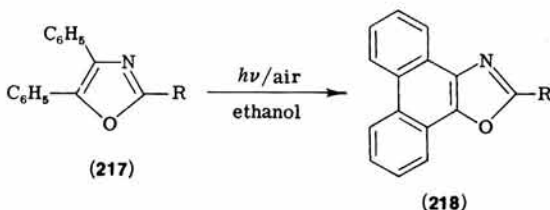
With fused-ring oxazoles of the type **211** imino anhydrides may be isolated in good yields in methanol. However, oxygenation in inert solvents such as methylene chloride takes an entirely different course and results in the formation of ω -cyano acids or esters. Photooxidation of fused-ring oxazoles unsubstituted in the 2-position, such as **213**, appears to proceed through the intermediate transannular peroxide **214**, which then undergoes intramolecular rearrangement¹⁷⁵ to form the cyano anhydride (**215**). Loss of CO from this mixed anhydride of formic acid leads to ω -cyano acid (**216**), the observed product, in 80–90% yields.¹²⁶



³⁶⁵ H. H. Wasserman, F. J. Vinick, and Y. C. Chang, *J. Amer. Chem. Soc.* **94**, 7180 (1972).

Reaction of oxazoles with singlet oxygen generated from the thermal decomposition of 9,10-diphenylanthracene peroxide gives oxidation products identical to those observed in dye-sensitized photooxygenations.³⁶⁶⁻³⁶⁸

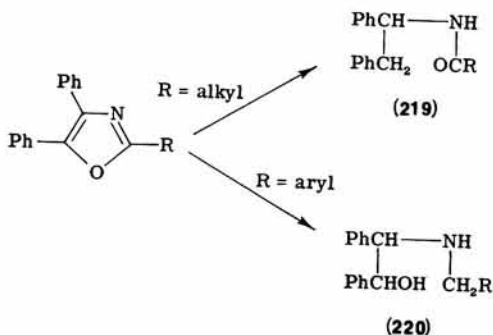
Unsensitized photolysis of 4,5-diphenyloxazoles (217) in ethanolic solution in air in the presence³⁶⁹ or absence³⁷⁰ of iodine leads to the formation of phenanthro[9,10-*d*]oxazoles (218).



F. MISCELLANEOUS RING CLEAVAGE REACTIONS

1. By Reduction

Chemical or catalytic reduction of oxazoles results in cleavage of the heterocyclic ring involving fission of the bond between C-2 or C-5 and oxygen; simple reduction products such as oxazolines or oxazolidines have never been isolated. Dornow and Eichholtz³⁷¹ have made some valuable



³⁶⁶ H. H. Wasserman and J. R. Scheffer, *J. Amer. Chem. Soc.* **89**, 3073 (1967).

³⁶⁷ J. L. Cooper, Ph.D. Thesis, Yale University (1970); *Diss. Abstr. B* **31**, 7182 (1971).

³⁶⁸ H. H. Wasserman, J. R. Scheffer, and J. L. Cooper, *J. Amer. Chem. Soc.* **94**, 4991 (1972).

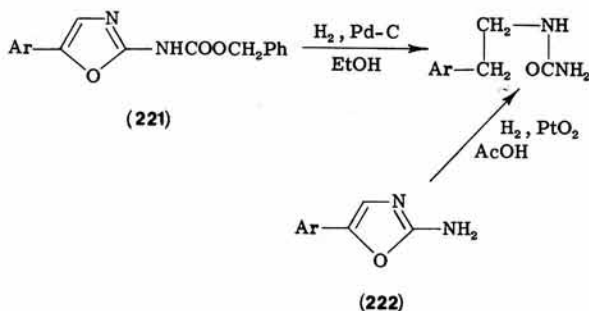
³⁶⁹ J. L. Cooper and H. H. Wasserman, *Chem. Commun.*, 200 (1969).

³⁷⁰ M. Kojima and M. Maeda, *Tetrahedron Lett.*, 2379 (1969).

³⁷¹ A. Dornow and H. Eichholtz, *Chem. Ber.* **86**, 384 (1953).

generalizations from a study on the behavior of 2-substituted 4,5-diphenyloxazoles toward reduction. With sodium and ethanol, the reduction product is an amide (**219**) when a 2-alkyl group is present, while an amino alcohol (**220**) is obtained when the 2-substituent is an aryl group. Catalytic hydrogenation over platinum always results in saturation of the aryl substituents prior to cleavage of the oxazole ring; uniformly the products are acid amides.³⁷¹ Reductive fission of 2,5-diphenyloxazole with sodium and ethanol,³⁷¹ or lithium aluminum hydride³⁷² in tetrahydrofuran gives phenyl benzylaminomethyl carbinol. 5-Phenyloxazole and 5-phenyl-2-oxazolecarboxylic ester, on the other hand, resist hydrogenation over palladium-carbon or platinum oxide.³⁷³ Similarly, ethyl 4-ethoxycarbonyl-2-aminoxazole-5-acetate (**44**) resisted hydrogenation over Raney nickel in ethanol.¹¹²

Hydrogenolysis of several substituted 2-, 4-, and 5-aminoxazole derivatives has been studied by Tanaka and his co-workers,³⁷³⁻³⁷⁶ Thus, hydrogenation of benzyl 5-aryloxazole-2-carbamates (**221**) or of 2-amino-5-aryloxazoles (**222**) over palladium-carbon in ethanol or platinum oxide in acetic acid gives 1-(2'-arylethyl)ureas.^{373,374}



Hydrogenation of **221** over platinum oxide in acetic acid leads to 1-benzyloxycarbonyl-3-(2'-arylethyl)urea in high yields.^{373,375} The bulky substituents present in the oxazole ring show a marked effect on ring fission.³⁷⁵ Reductive cleavage of benzyl 5-oxazolecarbamate using palladium-carbon in ethanol gives α -acylaminonitrile through the initially formed 5-aminoxazole, while the 4-oxazolecarbamates under similar conditions are converted to a brown resin.³⁷⁶ Reduction in acetic anhydride

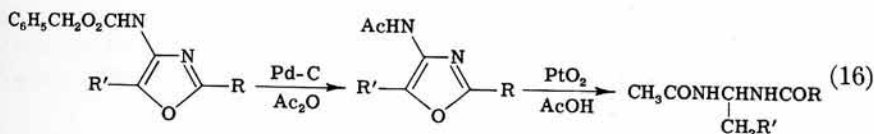
³⁷² N. G. Gaylord and D. J. Kay, *J. Amer. Chem. Soc.* **78**, 2167 (1956).

³⁷³ C. Tanaka, *Yakugaku Zasshi* **87**, 10 (1967).

³⁷⁴ C. Tanaka and H. Nishiki, *Yakugaku Zasshi* **87**, 14 (1967).

³⁷⁵ C. Tanaka, *Yakugaku Zasshi* **91**, 485 (1971).

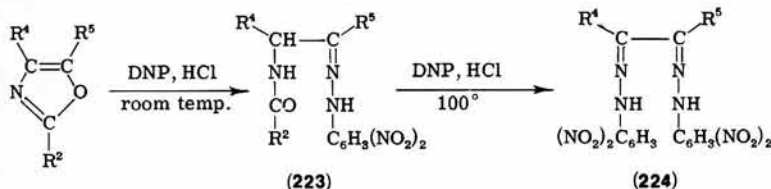
³⁷⁶ C. Tanaka and H. Asai, *Yakugaku Zasshi* **91**, 436 (1971).



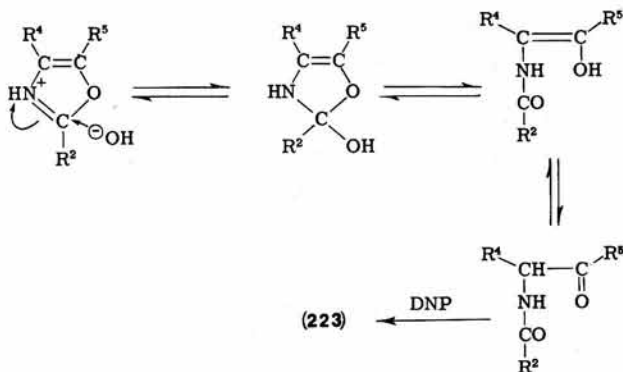
using palladium-carbon results in the formation of 4- or 5-acetamido-oxazoles, which are easily ring-cleaved to the corresponding bis amides [Eq. (16)].³⁷⁶

2. With 2,4-Dinitrophenylhydrazine

Many oxazoles react slowly at room temperature with 2,4-dinitrophenylhydrazine in hydrochloric acid to form hydrazones (223) by ring fission.^{84,160} On the other hand, refluxing results in the formation of osazones (224) of glyoxal derivatives, presumably via 223.³⁷⁷



Bredereck and his co-workers³⁷⁷ suggest that the reaction occurs by the mechanism of Scheme 11.



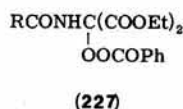
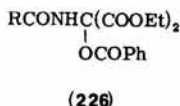
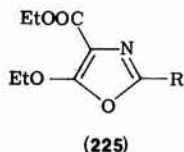
Scheme 11

3. By Other Methods

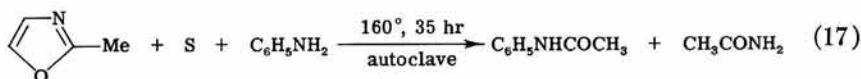
Theilig⁸⁴ has reported that 4,5-dimethyloxazole on treatment with benzoyl chloride in 10% sodium hydroxide yields 3-benzamidobutan-2-

³⁷⁷ H. Bredereck, R. Gompper, F. Reich, and U. Gotsmann, *Chem. Ber.* **93**, 2010 (1960).

one. Italian workers⁶² have found that the oxidative cleavage of 5-ethoxy-4-ethoxycarbonyloxazoles (**225**, R = H or Me) with benzoyl nitrate (from benzoyl chloride and silver nitrate) in chloroform gives **226**, while with perbenzoic acid the reaction gives the perbenzoate **227**.

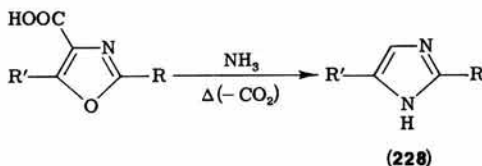


Reaction of 2-methyloxazole with sulfur and amines at 160° for 35 hours in an autoclave results in ring rupture. Thus, with aniline, acetanilide and acetamide are the products. It was suggested that the cleavage of the oxazole occurs at the 3-4 and 1-5 bonds [Eq. (17)].³⁷⁸



G. MISCELLANEOUS RING TRANSFORMATIONS

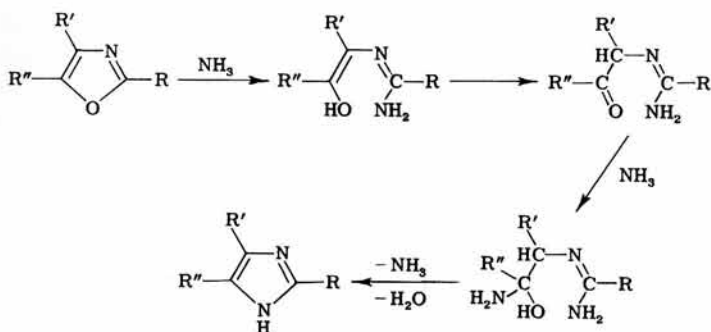
It has long been known that the conversion of oxazoles into imidazoles may be accomplished by treatment at high temperatures with ammonia or amines.^{132, 160, 379} Oxazole-4-carboxylic acids are converted similarly into the corresponding decarboxylated imidazoles (**228**).³⁰²



Many oxazoles, including those unsubstituted at position 2, have been transformed into imidazoles in good yields when heated at 180°–200° with formamide or formamide/ammonia in an autoclave.^{84, 120} The reaction fails with benzoxazole and 2,4,5-triethyloxazole. Bredereck *et al.*¹⁰ have postulated Scheme 12 as the reaction course for this transformation on the basis of an ammonolytic fission.

³⁷⁸ T. P. Sycheva and M. N. Shchukina, *Zh. Vses. Khim. Obschest.* **6**, 117 (1961); *Chem. Abstr.* **55**, 14461 (1961).

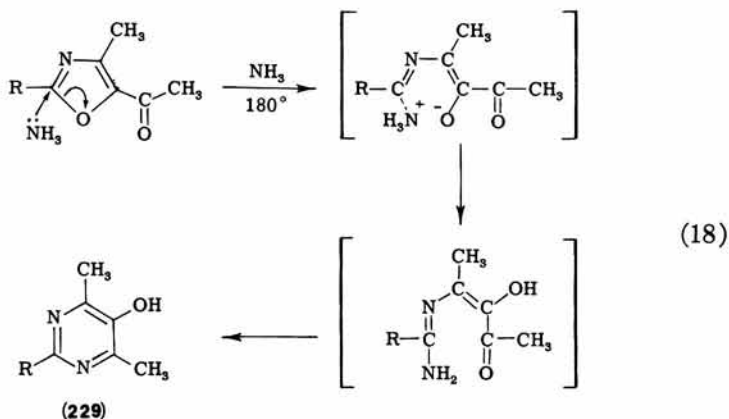
³⁷⁹ S. S. Minovici, *Ber.* **29**, 2097 (1896).



Scheme 12

Catalytic transformation of alkyl- or aryloxazoles into the corresponding thiazoles^{380,381} in low yields is possible by passage over alumina in a stream of hydrogen sulfide at 350°. This indicates that the oxazole ring is more stable towards attack by hydrogen sulfide than is furan.³⁸⁰

Acetyloxazoles are known to ring-open and recyclize in a number of interesting ways in the presence of nucleophilic reagents. Thus, with ammonia at 180°, 5-acetyloxazoles give 5-hydroxypyrimidines (**229**), probably by the reaction pathway shown in Eq. (18).³⁸²



Recently Ghosh and Ternai³⁸³ have reported the facile ring-opening and subsequent recyclization of 4- and 5-acetyloxazoles with the dicyano-

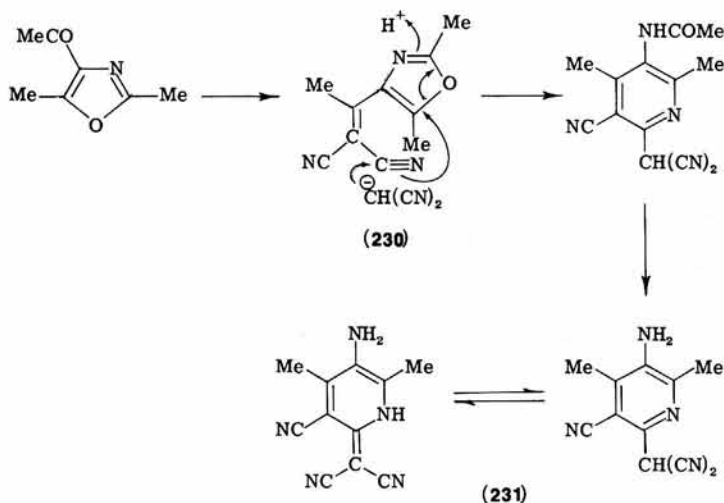
³⁸⁰ Yu. K. Yur'ev and I. G. Zhukova, *Zh. Obshch. Khim.* **28**, 7 (1958); *J. Gen. Chem. USSR* **28**, 5 (1958).

³⁸¹ R. L. Ellsworth, D. F. Hinkley, and E. F. Schoenewaldt, French Demande 2,011,993 (1970); *Chem. Abstr.* **74**, 3628 (1971).

³⁸² A. Dornow and H. Hell, *Chem. Ber.* **93**, 1998 (1960).

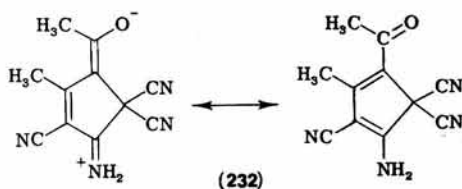
³⁸³ P. B. Ghosh and B. Ternai, *J. Org. Chem.* **37**, 1047 (1972).

methide anion. Thus, the reaction of 4-acetyl-2,5-dimethyloxazole with malononitrile in the presence of a base gives a red 3-aminopyridine derivative (**231**) through the intermediate formation of the dicyanovinyl compound (**230**), followed by an attack of a second molecule of malononitrile and concerted ring-opening of the oxazole ring as shown in Scheme 13.



Scheme 13

On the other hand, a similar reaction of 5-acetyl-4-methyl- or 5-acetyl-2,4-dimethyloxazole leads to 2-acetyl-5-amino-1,1,4-tricyano-3-methylcyclopentadiene (**232**), a yellow crystalline compound, in 60% yield. A mechanism of the formation of **232** has been proposed.³⁸³



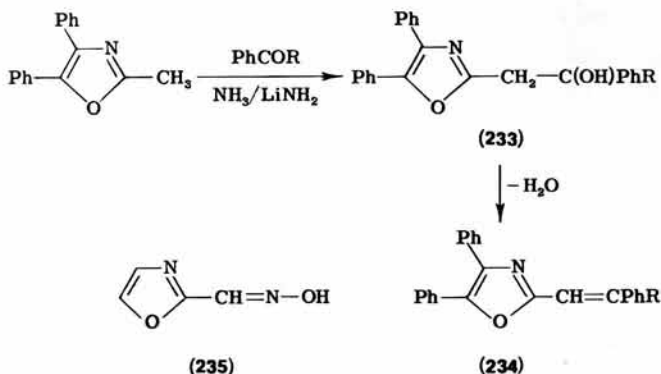
Derivatives of 1,2,4-triazine have been obtained by quaternization of the substituted oxazoles with alkyl *p*-toluenesulfonate above 100°, followed by treatment of the product with hydrazine hydrate in a solvent.³⁸⁴

³⁸⁴ O. P. Shvaika and V. I. Fomenko, USSR Patent 310,907 (1971); *Chem. Abstr.* **75**, 151843 (1971).

H. REACTIONS OF SUBSTITUENTS ON RING CARBON ATOMS

1. *Alkyl and Aryl Groups*

Methyl substituents in the 2-position of oxazoles, as in other azoles, are reactive toward electrophiles in the presence of bases, but those in the 4- and 5-positions act as if they were attached to a benzene ring.^{87, 121, 385} Accordingly, 2-methyl-4,5-diphenyloxazole condenses with benzaldehyde or benzophenone in liquid ammonia containing lithium amide, to form 2-(β -hydroxyethyl) derivatives (**233**, R = H or Ph) which on dehydration give 2-styryl oxazoles (**234**).³⁸⁵ The 2-methyl group in benzoxazoles and



4,5,6,7-tetrahydrobenzoxazole reacts similarly with aromatic aldehydes.³⁸⁵⁻³⁸⁷ Another reaction of a methyl substituent is the transformation of 2-methyloxazole into 2-hydroxyiminomethyloxazole (**235**) in low yield by treatment with pentyl nitrite and sodamide in liquid ammonia.³⁸⁸

In the case of 4-methyl-2,5-disubstituted oxazoles, bromination with either bromine or *N*-bromosuccinimide affords the 4-bromomethyl compound.³⁰⁷ 2-Bromomethyl-4,5-diphenyloxazole is obtained by bromination of the corresponding oxazole with NBS in the presence of dibenzoyl peroxide.¹²¹ Reaction with phosphorus pentachloride similarly gives the side-chain-chlorinated products.⁶⁰

³⁸⁵ V. Dryanska and Khr. Ivanov, *God. Sofii. Univ. Khim. Fak.* 1968-69 **63**, 105 (1971); *Chem. Abstr.* **76**, 126844 (1972).

³⁸⁶ H. G. Thompson and M. B. Bochner, Belgian Patent 659,424 (1965); *Chem. Abstr.* **64**, 2090 (1966).

³⁸⁷ S. Ueno, E. Shimogo, T. Kawasaki, D. Inmaru, F. Hirose, S. Heya, Y. Omura, and T. Fujii, German Offen. 2,026,452 (1970); *Chem. Abstr.* **74**, 42349 (1971).

³⁸⁸ R. H. Good and G. Jones, *J. Chem. Soc. C*, 1938 (1970).

The reactions of aryl substituents, which are electrophilic substitutions, have been described in Section IV.B.

2. Hydroxyalkyl and Haloalkyl Groups

Hydroxyalkyl groups can easily be converted into haloalkyl groups using thionyl chloride or phosphorus pentabromide.^{97, 103, 389, 390} The haloalkyloxazoles undergo the usual reactions of alkyl halides, the halogen atom being replaceable by hydroxy,^{121, 146} alkoxy,^{60, 99, 308} cyano,^{42, 103, 389} substituted amino,^{31, 32, 60, 85, 146, 308, 389} and mercapto¹⁴⁶ groups. A dichloromethyl group is transformed into an aldehyde on successive treatment with sodium methoxide and with aqueous acid.⁶⁰

3. Aldehyde and Ketone Groups

Several oxazole-4-aldehydes have been described, while only one oxazole-2-aldehyde is known so far;^{2, 4} they are fairly stable to oxidation by air. Since the oxazoles are not known to undergo Friedel-Crafts acylation, ketone substituents are introduced indirectly into the nucleus, either before the ring is formed^{40, 382, 391} or by modification of substituents already present.¹⁴⁷ 4-Acetyloxazoles are oxidized to the corresponding acids with sodium hypobromite.¹⁴⁷ Both oxazolyl aldehydes and ketones form derivatives with hydroxylamine, phenylhydrazine, etc., as expected.

4. Carboxylic Acid and Ester Groups

The kinetics and mechanism of the decarboxylation of 5-(*p*-substituted phenyl)-2-oxazolecarboxylic acids in neutral, acidic, and basic media have been studied by Tanaka.³⁹² In quinoline or in dichloroacetic acid as a nonaqueous solvent, the reaction shows first-order kinetics.³⁹² Studies on the decarboxylation of oxazolium (and other related azolium) carboxylates indicate that both 2- and 5-acids decarboxylate through their zwitterionic tautomers.³⁹³ Heating an oxazole-2-carboxylic acid at or above its melting point may also result in decarboxylation.^{29, 394}

Oxazolecarboxylic acids are readily converted into acid chlorides,^{302, 395, 396}

³⁸⁹ A. B. A. Jansen and M. Szelke, *J. Chem. Soc.*, 405 (1961).

³⁹⁰ U. H. A. Lindberg and P. E. Saeter, French Patent M3008 (1965); *Chem. Abstr.* **62**, 11818 (1965).

³⁹¹ A. Treibs and W. Sutter, *Chem. Ber.* **84**, 96 (1951).

³⁹² C. Tanaka, *Yakugaku Zasshi* **85**, 193 (1965); *Chem. Abstr.* **62**, 16222 (1965).

³⁹³ P. Haake, L. P. Bausher, and J. P. McNeal, *J. Amer. Chem. Soc.* **93**, 7045 (1971).

³⁹⁴ K. Shirai and O. Aki, Japanese Patent 18774 (1968); *Chem. Abstr.* **70**, 68343 (1969).

³⁹⁵ T. P. Sycheva, T. Kh. Trupp, and M. N. Shchukina, *Zh. Obshch. Khim.* **32**, 2882 (1962); *J. Gen. Chem. USSR* **32**, 2839 (1962).

³⁹⁶ D. M. O'Mant, British Patent 1,139,940 (1969); *Chem. Abstr.* **70**, 106494 (1969).

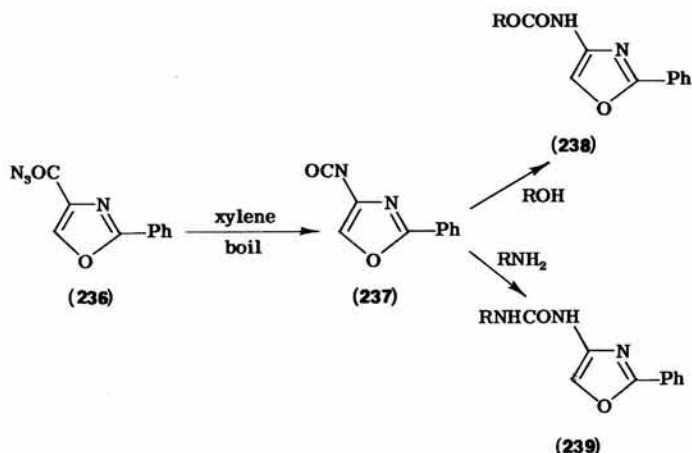
amides,^{61, 388, 395, 397} and esters and hydrazides^{27, 30, 61, 131, 397} by usual procedures. They may also be reduced to alcohols with lithium aluminum hydride^{103, 389} or sodium borohydride^{389, 396} via either their esters or the acid chlorides. 5-Methyl-2-phenyloxazole-4-carboxylic acid has been converted by the Rosenmund reduction of the acid chloride into the corresponding aldehyde.³⁰²

Reaction of 2-phenyloxazole-4-carbonyl chloride with diazomethane affords the crystalline diazomethyl ketone, which fails to undergo the Wolff rearrangement.³⁸⁹ In general the esters are smoothly hydrolyzed by aqueous alkali, but attempts to hydrolyze 5-aminooxazole-4-carboxylates result in disruption of the ring system.³⁸⁹ The behavior of oxazole-4-carboxylic acids has been described in greater detail in "The Chemistry of Penicillin".²

5. Acid Amides and Azides

N-Unsubstituted carboxamides are dehydrated to nitriles on treatment with phosphorus pentoxide or phosphoryl chloride.^{161, 388, 398, 399} N,N-Disubstituted carboxamides on reduction with lithium aluminum hydride give the corresponding dialkylaminomethyloxazoles.³⁸⁹

Acid azides are obtainable by reaction of the respective hydrazides with nitrous acid or of acid chlorides with sodium azide.^{302, 376} Curtius degradation of 2-phenyloxazole-4-carbonyl azide (**236**) in boiling xylene



³⁹⁷ E. Marchetti, German Offen. 2,110,363 (1971); *Chem. Abstr.* **75**, 151776 (1971).

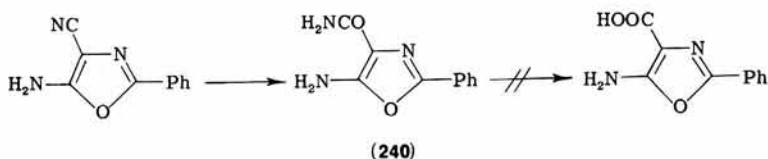
³⁹⁸ T. P. Sycheva, T. Kh. Trupp, and M. N. Shchukina, *Zh. Obshch. Khim.* **32**, 3666 (1962); *J. Gen. Chem. USSR* **32**, 3597 (1962).

³⁹⁹ G. O. Chase, U.S. Patent 3,222,374 (1965); *Chem. Abstr.* **64**, 6657 (1966).

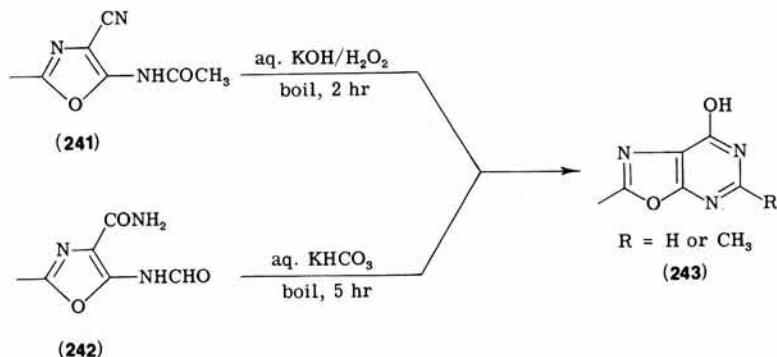
gives the crystalline isocyanate (237) which offers a convenient route to carbamates (238) and *N,N'*-disubstituted ureas (239) on reaction with alcohols^{302, 376, 389} and amines,³⁸⁹ respectively.

6. Cyanide Groups

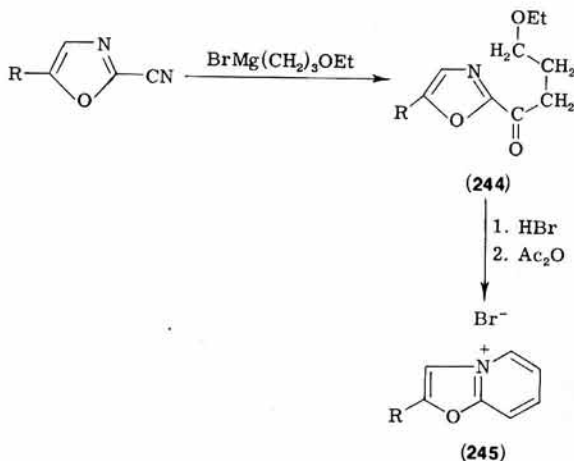
Oxazoles substituted with a cyano group in the 2-, 4-, and 5-positions are known; many of these can be reduced to aldehydes by the Stephen method² and hydrolyzed by alkali to the related amides and carboxylic acids. 2-Phenyl-5-aminooxazole-4-carbonitrile on treatment with concentrated sulfuric acid forms the crystalline amide (240); further hydrolysis, however, is unsuccessful. The corresponding 4-carboxylic esters are also stable to hydrolysis.³⁸⁹



4-Cyano- or 4-carboxamidooxazoles having acylamino groups at position 5 can be cyclized to the respective oxazolo[5,4-*d*]pyrimidine-7-ols in the presence of base.^{200, 389} Thus 241 or 242 gives 243.



5-Substituted 2-cyanooxazoles react with 3-ethoxypropylmagnesium bromide to give the corresponding 2-(4-ethoxybutyryl)oxazoles (244), which when heated with 48% hydrobromic acid, followed by treatment with acetic anhydride, are cyclized and aromatized to form 2-substituted oxazolo[3,2-*a*]pyridinium bromides (245) in excellent yields.³⁸⁸



7. Nitro Groups

To our knowledge only one nitrooxazole (166) where a nitro group is directly attached to the nucleus appears to have been reported.¹⁰⁴ The reduction of nitrophenyl- to aminophenyloxazoles has often been carried out either chemically or catalytically, the preferred reagents being stannous chloride,³⁰⁴ tin and hydrochloric acid,^{161, 398} sodium sulfide,³⁰⁴ and hydrogen with Raney nickel.^{304, 310} These reagents indirectly illustrate the stability of the oxazoles towards reduction. The aminophenyloxazoles can be diazotized; the diazonium salts are fairly stable, and undergo normal substitution reactions.³⁰⁴

8. Amino Groups

Oxazoles with a free amino group in position 4 are most probably not yet known (but derivatives such as urethanes and ureas are known, e.g., 238 and 239), whereas the 2-amino- and 5-aminoxazoles are numerous. They easily afford acyl⁴⁰⁰ and arylsulfonyl^{112, 401} derivatives, and react with isothiocyanates to give the corresponding thioureas.⁴⁰² The amino substituent in position 2 could not be diazotized,¹⁰⁴ which may be explained on the basis of the relatively high positive net charge already present at C-2.²²⁸

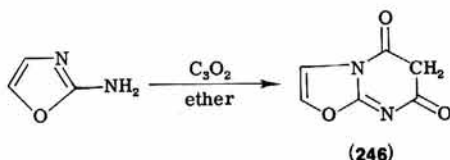
The reaction of carbon suboxide with 2-aminoxazoles, which are

⁴⁰⁰ G. Crank, British Patent 1,264,258 (1972); *Chem. Abstr.* **76**, 126963 (1972).

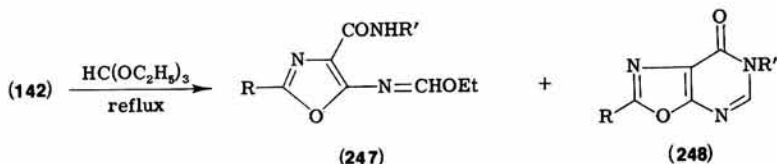
⁴⁰¹ G. Griss, E. Kutter, W. Grell, and U. Harding, German Offen. 1,926,558 (1970); *Chem. Abstr.* **74**, 42348 (1971).

⁴⁰² G. Crank, German Offen. 2,036,193 (1971); *Chem. Abstr.* **74**, 141750 (1971).

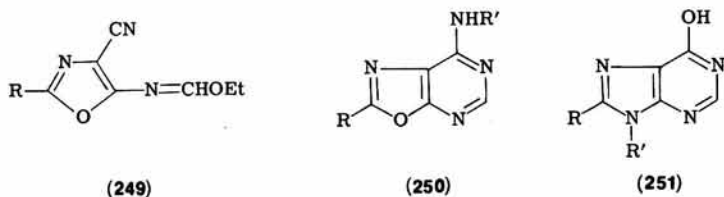
formally capable of amine-imine tautomerism, leads to the formation of coupled heterocyclic systems containing the dioxotetrahydropyrimidine ring.⁴⁰³ Thus, **246** is obtained by passing carbon suboxide into a solution of 2-aminooxazole in ether.



5-Aminooxazole-4-carboxamides (**142**) on refluxing with ethyl orthoformate yield the corresponding 5-ethoxymethyleneaminooxazole-4-carboxamides (**247**), together with oxazolo[5,4-*d*]pyrimidines (**248**), formed by ring closure.¹⁹⁹ Alternatively, the ethoxymethylene derivatives (**247**) can smoothly be converted into **248** when refluxed with acetic anhydride.



The reaction of 5-ethoxymethyleneamino-4-cyanooxazoles (**249**) with primary amines gives 7-substituted aminooxazolo[5,4-*d*]pyrimidines (**250**); when an excess of amine was used, substituted hypoxanthines (**251**) were the products.⁴⁰⁴



Under normal conditions, aminooxazoles do not exhibit amine-imine tautomerism. 2-Aminooxazoles have been found to be largely in the

⁴⁰³ L. B. Dashkevich and E. S. Korbelainen, *Zh. Obshch. Khim.* **34**, 3427 (1964); *J. Gen. Chem. USSR* **34**, 3470 (1964).

⁴⁰⁴ Y. Otsuka, Japanese Patent 21,434 (1972); *Chem. Abstr.* **77**, 101,650 (1972).

primary amino form by comparison of their ultraviolet absorption spectra with those of appropriately blocked derivatives.³¹⁶ A recent SCF-MO study of the tautomerism of 2-anilinoxazole also shows that the amino form predominates.⁴⁰⁵ Likewise, both infrared and NMR spectroscopic data confirm the primary amino structure of 5-aminooxazoles.²⁰¹

9. Hydroxyl and Mercapto Groups

Hydroxyoxazoles are known to exist predominantly in the keto form and are commonly called oxazolones, or (preferably) oxazolinones. Existing experimental evidence, particularly from ultraviolet and infrared spectroscopy, confirms this. Since the literature on the chemistry of oxazolinones is extensive, comprehensive coverage would be beyond the scope of the present review. For further information, the reader is referred to the works of Lur'e and Chaman,⁴⁰⁶ and of Filler.⁴⁰⁷

Mercaptooxazoles resemble the hydroxy compounds in that they exist predominantly in the tautomeric thione form. The position of the thione-thiol equilibrium has been studied by Kjellin and Sandström,²⁴⁵ and tautomeric ratios in the range (10^5 – 10^8):1 have been obtained. Methods of preparation of oxazolin-2-thiones and their *N*- and *S*-alkyl derivatives have been described.^{408–414} Isomerization of *S*-alkyl to *N*-alkyl compounds can be achieved when the former are heated with mercuric bromide in toluene.⁴¹²

10. Halo Groups

The formation and some displacement reactions of halooxazoles have been discussed earlier in this review (Sections IV, B and C). Catalytic hydrogenation of halooxazoles gives the corresponding oxazole; simultaneous side-chain dehalogenation may also occur.^{60, 171}

⁴⁰⁵ N. Bodor, I. Schwartz, and N. Trinajstić, *Z. Naturforsch. B* **26**, 400 (1971).

⁴⁰⁶ S. I. Lur'e and E. S. Chaman, *Reakts. Metody Issled. Org. Soedin.* **9**, 155 (1959).

⁴⁰⁷ R. Filler, *Advan. Heterocycl. Chem.* **4**, 75–106 (1965).

⁴⁰⁸ F. Weygand, H. J. Bestmann, and F. Steden, *Chem. Ber.* **91**, 2537 (1958).

⁴⁰⁹ J. Willems and A. Vandenbergh, *Bull. Soc. Chim. Belg.* **69**, 517 (1960).

⁴¹⁰ E. D. Sych and Zh. N. Belaya, *Zh. Obshch. Khim.* **33**, 1507 (1963); *J. Gen. Chem. USSR* **33**, 1471 (1963).

⁴¹¹ G. Kjellin and J. Sandström, *Acta Chem. Scand.* **23**, 2879 (1969).

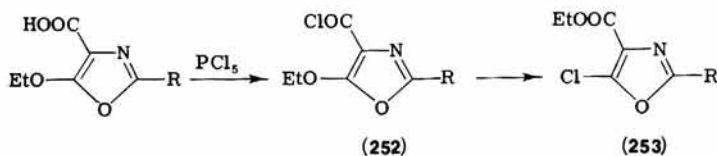
⁴¹² P. Nuhn and G. Wagner, *Arch. Pharm. (Weinheim)* **301**, 186 (1968).

⁴¹³ E. D. Sych, Zh. N. Belaya, and O. V. Moreiko, *Khim. Geterotsikl. Soedin., Sb. 2: Kislorodsoderzhashchie Geterotsikly*, 282 (1970); *Chem. Abstr.* **76**, 140606 (1972).

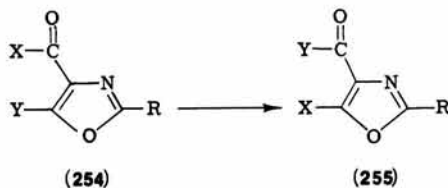
⁴¹⁴ G. Lacasse and J. M. Muchowski, *Can. J. Chem.* **50**, 3082 (1972).

I. REARRANGEMENTS

It has been reported^{2, 61} that 2-substituted 5-ethoxyoxazole-4-carboxylic acids on treatment with phosphorus pentachloride give the corresponding acid chlorides (**252**), which rearrange spontaneously or on heating to the 5-chlorooxazole-4-carboxylates (**253**).

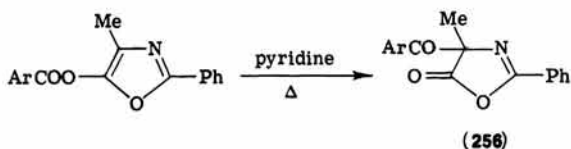


In general, oxazole derivatives of the type **254** (when X = H, Y = OH or Cl; when X = Cl or NH₂, Y = OEt) rearrange on heating to **255** through ring-opening and recyclization in the alternative manner.² Thus, the isomerization of 4-(α -hydroxyalkylidene)oxazole-5-ones to oxazole-4-carboxylic acids may be regarded as a special case of this rearrangement (Section II,P).



where R = alkyl or aryl

Pines and Sletzinger^{415, 416} have found that the rearrangement of 2,4-disubstituted 5-acyloxyoxazoles occurs on heating in the presence of pyridine, yielding 4-acyl-2-oxazolin-5-one derivatives (**256**).



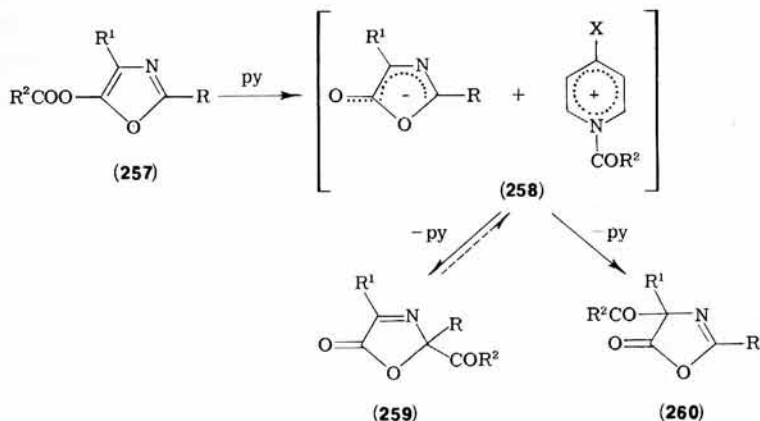
In another investigation, 5-acyloxyoxazoles (**257**) were found to rearrange to 2- and 4-acyl-5-oxazolinones (**259** and **260**).⁴¹⁷ The reaction in the presence of 4-dimethylaminopyridine proceeds 20,000 times faster

⁴¹⁵ S. H. Pines and M. Sletzinger, *Tetrahedron Lett.*, 727 (1969).

⁴¹⁶ S. H. Pines and M. Sletzinger, U.S. Patent 3,676,453 (1972); *Chem. Abstr.* 77, 101565 (1972).

⁴¹⁷ W. Steglich and G. Hoeffle, *Tetrahedron Lett.*, 4727 (1970).

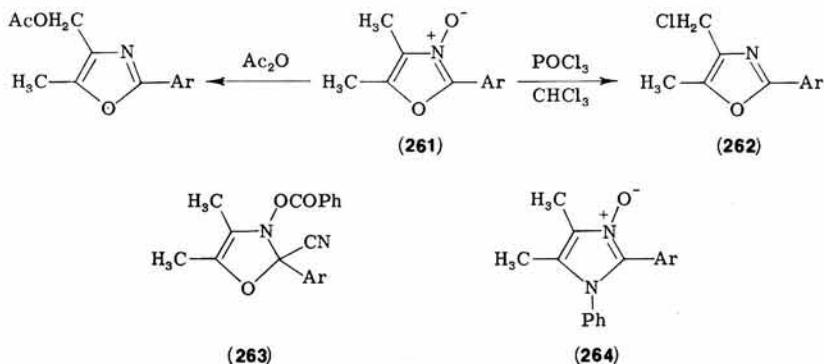
than with pyridine, when it was suggested to occur through the ion pair (258).



V. Oxazole *N*-Oxides

The synthesis of oxazole *N*-oxides from α -hydroxyimino ketones and aldehydes, and their reductive conversion into oxazoles has already been described (Section II, K). Attempted *N*-oxidation of 2,5-diphenyloxazole with hydrogen peroxide in acetic acid failed; it led to ring-opening.⁴¹⁸ Oxazole *N*-oxides show a strong absorption band around 1240 cm^{-1} in their infrared spectra, indicative of an aromatic *N*-oxide group.⁴¹⁹ Recently, NMR data for several oxazole *N*-oxides have been reported.¹⁴⁸

A 4-methyl group in 2-aryloxazole *N*-oxides (261) is subject to easy nucleophilic attack in reactions with phosphorus oxychloride and acetic

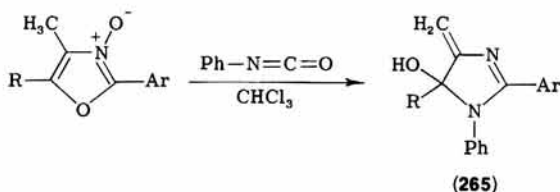


⁴¹⁸ V. N. Kerr, D. G. Ott and F. N. Hayes, *J. Amer. Chem. Soc.* **82**, 186 (1960).

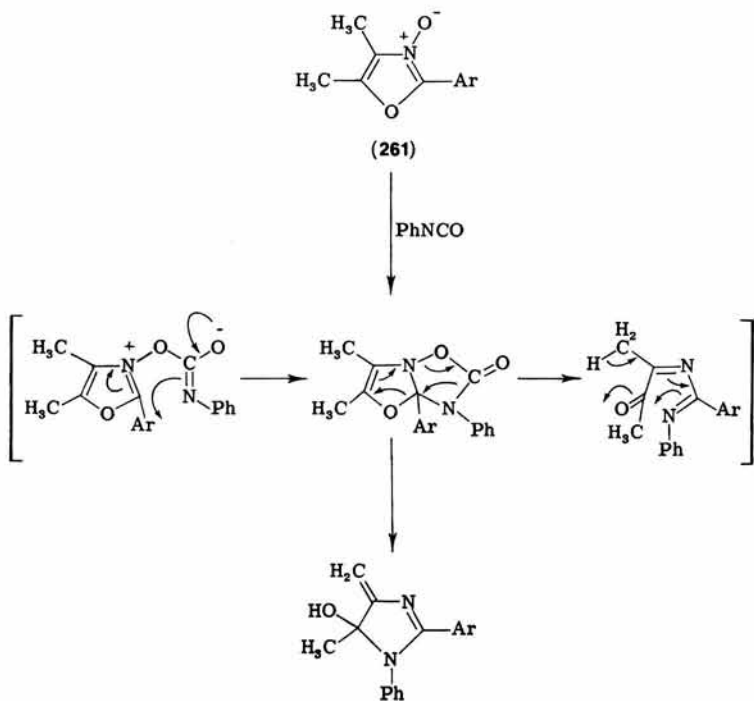
⁴¹⁹ Y. Goto, M. Yamazaki, and M. Hamana, *Chem. Pharm. Bull.* **19**, 2050 (1971).

anhydride, while a 5-methyl group is inert.⁴¹⁹ Treatment of oxazole *N*-oxides with phosphorus trichloride in chloroform gives both the normal deoxygenated product and the 4-chloromethyloxazole (e.g., **262**).^{146, 419}

The formation of Reissert compounds (**263**) of oxazole *N*-oxides (reaction with potassium cyanide and benzoyl chloride) have been reported.⁴²⁰



The structure of the product obtained by Diels and Riley¹⁴³ from the reaction of oxazole *N*-oxide and phenyl isocyanate, and reformulated by Cornforth and Cornforth¹⁶⁰ as the imidazole 3-oxide structure **264**, has recently been questioned by Japanese workers.⁴²¹ Investigations by



Scheme 14

⁴²⁰ Y. Goto and M. Yamazaki, *Chem. Pharm. Bull.* **18**, 756 (1970).

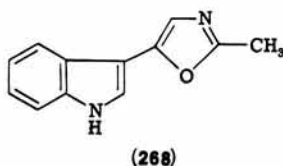
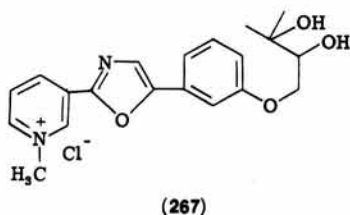
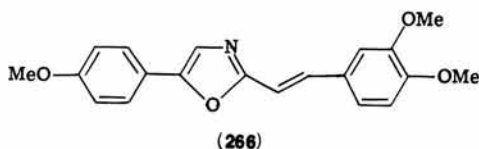
⁴²¹ Y. Goto, N. Honjo, and M. Yamazaki, *Chem. Pharm. Bull.* **18**, 2000 (1970).

NMR and mass spectroscopy indicate that it is 5-hydroxy-4-methylene-4,5-dihydroimidazole (265).

The formation of 265, $R = CH_3$, is rationalized as the addition of the $C=N$ of phenyl isocyanate across the formal nitron function of the oxazole *N*-oxide (261), followed by opening of the oxazole ring, decarboxylation, and recyclization (Scheme 14).⁴²¹

VI. Naturally Occurring Oxazoles

Some fluorescent alkaloids containing the oxazole nucleus have been isolated from certain species of Gramineae and Rutaceae. Annuloline (266), obtained from the roots of *Lolium multiflorum*, an annual rye grass,^{422, 423} and *N*-methylhalfordinium chloride (267) and halfordinol (48) from the bark of *Halfordia scleroxyla*⁴²⁴ are the first representative members of this group of alkaloids. Two short reviews^{425, 426} concerning the occurrence of annuloline in *Lolium* and its fluorescence are noteworthy.



The mold metabolite, pimprinine (268), obtained from *Streptomyces pimprina*, is another naturally occurring oxazole.⁴²⁷

⁴²² R. S. Karimoto, Ph.D. Thesis, Purdue University (1962); *Diss. Abstr.* **23**, 2311 (1963).

⁴²³ R. S. Karimoto, B. Axelrod, J. Wolinsky, and E. D. Schall, *Tetrahedron Lett.*, 83 (1962); *Phytochemistry* **3**, 349 (1964).

⁴²⁴ W. D. Crow and J. H. Hodgkin, *Tetrahedron Lett.*, 85 (1963); *Aust. J. Chem.* **17**, 119 (1964).

⁴²⁵ W. Nitzsche, *Saatgut-Wirt.* **18**(12), 409-410 (1966); *Chem. Abstr.* **67**, 88258 (1967).

⁴²⁶ H. H. Schmidt, *Landwirt. Forsch.* **20**(1), 40-56 (1967); *Chem. Abstr.* **68**, 18813 (1968).

⁴²⁷ B. S. Joshi, W. I. Taylor, B. S. Bhate, and S. S. Karmarkar, *Tetrahedron* **19**, 1437 (1963).

Heteroaromatic *N*-Imines

HANS-JOACHIM TIMPE

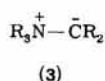
*Technische Hochschule für Chemie "Carl Schorlemmer" Leuna-Merseburg,
Sektion Verfahrenchemie, Merseburg, German Democratic Republic*

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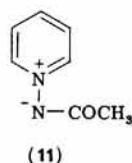
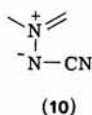
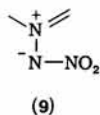
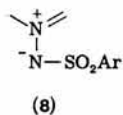
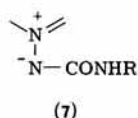
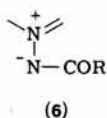
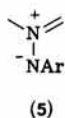
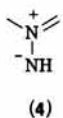
I. Introduction and Nomenclature

Amine *N*-imines are derived formally from tertiary amines by replacing the free pair of electrons by an imino group. Aliphatic, aromatic, or heteroaromatic compounds are obtained according to the nature of the amine. Heteroaromatic *N*-imines are derived from heterocyclic compounds containing an azomethine nitrogen atom in the molecule.

The *N*-imines are members of the isoelectronic and isosteric series: *N*-oxides, *N*-imines, and *N*-ylids (formulas 1-3). Whereas the *N*-oxides^{1,2} and the *N*-ylids³⁻⁵ have been reviewed several times, a detailed review of *N*-imines⁶ was published only recently; see also a brief summary in Sisler *et al.*⁷ Thus information is sparse for the amine *N*-imines, in contrast with the other members of the isosteric series.



The number of papers published on *N*-imines is relatively small. Efficient methods of preparation were not discovered until recently, and only since 1965 has the study of the *N*-imines been pursued to any extent. Nevertheless, *N*-imines have been known hitherto only as derivatives of pyridines, quinolines, isoquinolines, benzocinnolines, *v*-triazoles, *s*-triazoles, and thiazoles. *N*-Imines can be classified not only by the heterocyclic nucleus but also according to the substituent at the exocyclic imino group. Unsubstituted *N*-imines (4), *N*-arylimines (5), *N*-acylimines (6), *N*-carbamoylimines and *N*-thiocarbamoylimines (7), *N*-sulfonylimines (8), *N*-nitrocarbamoylimines (9), *N*-sulfonylimines (10), *N*-nitroimines (9), and *N*-cyanoimines (10) have all been synthesized.



The present review summarizes work published up to December 1971. Unfortunately, several nomenclatures are used in the literature for the

¹ E. Ochiai, "Aromatic N-Oxides." Elsevier, Amsterdam, 1967.

² A. R. Katritzky and J. M. Lagowski, "Heteroaromatic N-Oxides." Academic Press, New York, 1970.

³ A. W. Johnson, "Ylid Chemistry." Academic Press, New York, 1966.

⁴ W. K. Musker, *Fortschr. Chem. Forsch.* **14**, 295 (1970).

⁵ P. A. Love, *Chem. Ind. (London)*, 1070 (1970).

⁶ H.-J. Timpe, *Z. Chem.* **12**, 250 (1972).

⁷ H. H. Sisler, G. M. Omietanski, and B. Rudner, *Chem. Rev.* **57**, 1021 (1957).

class of compounds we designate as amine *N*-imines: thus, the following versions are found for the *N*-imine (11): pyridine 1- (or *N*-) acetylimide, 1-acetyliminopyridinium ylid, *N*-acetyliminopyridinium betaine, *N*-acetyliminopyridine, and 1-acetylamino-pyridinium hydroxide inner salt. In this review, the *N*-imine nomenclature will be used uniformly. This has advantages: (1) it expresses the isoelectronic relationship to the *N*-oxides; (2) the imine nomenclature is already in general use for the azomethine imine system which is the parent structural element of this class of compound.

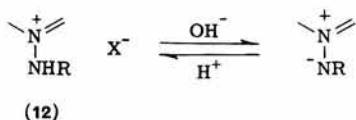
II. General Syntheses of Heteroaromatic *N*-Imines

General methods of preparation of heteroaromatic *N*-imines are beginning to be recognized, but they have not yet been widely applied. In addition, several special methods exist which have been used only for one specific heterocycle. Given this situation, the methods of preparation are classified in this chapter according to the parent heterocycle. The four most general methods of preparation are discussed in detail under the pyridine *N*-imines since this is where the experimental material is most extensive.

A. PYRIDINE *N*-IMINES

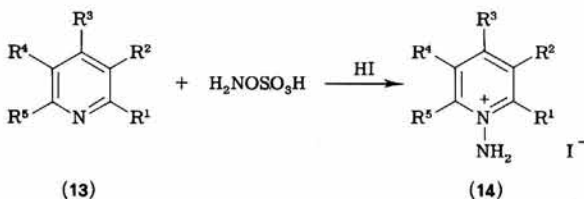
1. Preparation from Quaternary Pyridinium Salts

A common method of preparation of heteroaromatic *N*-imines is the deprotonation of the corresponding *N*-aminoimmonium salts (12). Most of the pyridine *N*-imines synthesized have been obtained by this method. The strength of base necessary for deprotonation depends on the substituent *R* in the salts (12) (see Section III,F). For instance, dilute aqueous alkali is sufficient for *N*-acyl-, *N*-sulfonyl-, and *N*-carbamoylimines, but concentrated alkali must be used for unsubstituted *N*-imines. Unsubstituted pyridine *N*-imines have only been detected by spectroscopic methods in solution (see Section III,B, and III,D).

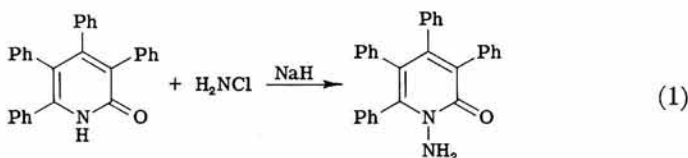


N-Aminopyridinium salts (14) can be prepared in various ways. A

very efficient method, described by Gösl and Meuwsen,^{8,9} utilizes aqueous solutions of pyridines (13) and hydroxylamine-*O*-sulfonic acid to give the quaternary salts (14) in satisfactory yield. From these salts, other salts can be obtained by anion exchange. The amination reaction fails^{9a} with some substituted pyridines (e.g., 3- and 4-ethoxycarbonylpyridine) but is nevertheless of wide applicability.¹⁰⁻¹⁹



The amination of pyridines to *N*-amino quaternary salts (14) has not yet succeeded with chloramine, which is another typical reagent for aminations. However, amination of pyridones has been described, as in Eq. (1).^{20,21}



N-Aminopyridinium salts (14) have been acylated with acid chlorides and anhydrides, and sulfonated with sulfonyl chlorides.^{10,13,14,17,22} Sul-

⁸ R. Gösl and A. Meuwsen, *Chem. Ber.* **92**, 2521 (1959); *Angew. Chem.* **69**, 754 (1957).

⁹ R. Gösl and A. Meuwsen, *Org. Syn.* **43**, 1 (1963).

^{9a} M. H. Palmer and P. S. McIntyre, *Tetrahedron Lett.*, 2147 (1968).

¹⁰ T. Okamoto, M. Hirobe, Y. Tamai, and E. Yabe, *Chem. Pharm. Bull.* **14**, 506 (1966).

¹¹ T. Okamoto, M. Hirobe, and A. Ohsawa, *J. Pharm. Bull. Jap.* **14**, 518 (1966).

¹² T. Okamoto, M. Hirobe, C. Mizushima, and A. Ohsawa, *J. Pharm. Soc. Jap. (Yakugaku Zasshi)* **83**, 308 (1963).

¹³ T. Okamoto, M. Hirobe, and E. Yabe, *Chem. Pharm. Bull.* **14**, 523 (1966).

¹⁴ K. T. Potts, H. R. Burton, and J. Bhattacharyya, *J. Org. Chem.* **31**, 260 (1966).

¹⁵ J. E. Downes, *J. Chem. Soc. C*, 2192 (1967).

¹⁶ V. Cullum, J. B. Farmer, and B. L. Hardley, *J. Pharmacol. Chemother.* **31**, 435 (1967).

¹⁷ J. Epszajn, E. Lunt, and A. R. Katritzky, *Tetrahedron* **26**, 1665 (1970).

¹⁸ T. Sasaki, K. Kanematsu, A. Kakehi, I. Ichikawa, and K. Hayakawa, *J. Org. Chem.* **35**, 426 (1970).

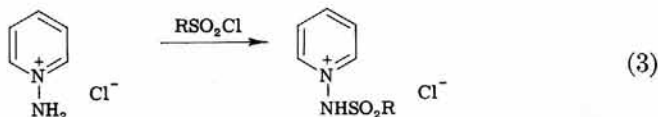
¹⁹ Balasubramanian, J. M. McIntosh, and V. Snieckus, *J. Org. Chem.* **35**, 433 (1970).

²⁰ K. Hoegerle, *Helv. Chim. Acta* **41**, 539 (1958).

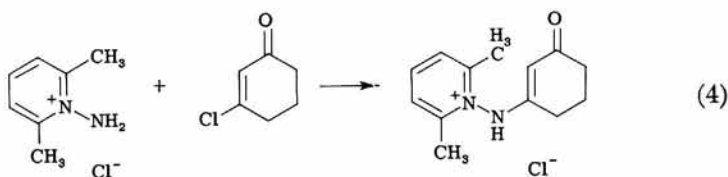
²¹ C. W. Rees and M. Yelland, *J. Chem. Soc. Perkin Trans. I*, 77 (1972).

²² J. A. Moore and J. Binkert, *J. Amer. Chem. Soc.* **81**, 6045 (1959).

fonation and acylation can occur with aliphatic as well as with aromatic acid derivatives [Eqs. (2), (3)].



Substitution reactions on the amino group of the salts have also been described with β -chlorovinyl ketones^{23,24} [Eq. (4)].



N-(2,4-Dinitrophenyl)pyridinium chlorides ("Zincke salts"^{10,25,26}; **15**) are starting materials for another preparation of *N*-aminopyridinium salts. Zincke salts react with hydrazines, aryl hydrazines, acyl hydrazines, and semicarbazides to form 5-(2,4-dinitroanilino)-2,4-pentadienal hydrazones and semicarbazones, respectively, by ring-opening.^{17,25,27-32} The recyclization of these compounds (**16**) with molar quantities of acids yields the quaternary salts **17** and 2,4-dinitroaniline.

²³ Y. Tamura, N. Tsujimoto, and M. Ikeda, *J. Chem. Soc. D*, 310 (1971).

²⁴ Y. Tamura, N. Tsujimoto, Y. Sumida, and M. Ikeda, *Tetrahedron* **28**, 21 (1972).

²⁵ T. Zincke, G. Heuser, and W. Möller, *Ann.* **333**, 296 (1904).

²⁶ A. F. Vompe and N. F. Turitsyana, *Zh. Obshch. Khim.* **27**, 3282 (1957); *Chem. Abstr.* **52**, 9112 (1958).

²⁷ S. F. Dufton, *J. Chem. Soc.* **61**, 785 (1892).

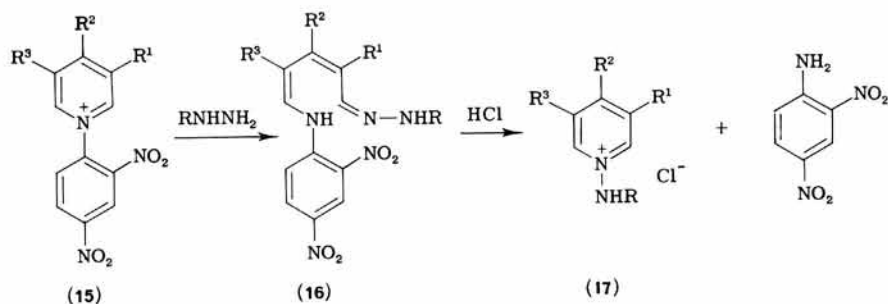
²⁸ W. H. Perkin and R. Robinson, *J. Chem. Soc.* **103**, 1978 (1913).

²⁹ H. Beyer, K. Leverenz, and H. Schilling, *Angew. Chem.* **73**, 272 (1961).

³⁰ H. Beyer and E. Thieme, *J. Prakt. Chem.* [4], **31**, 293 (1966).

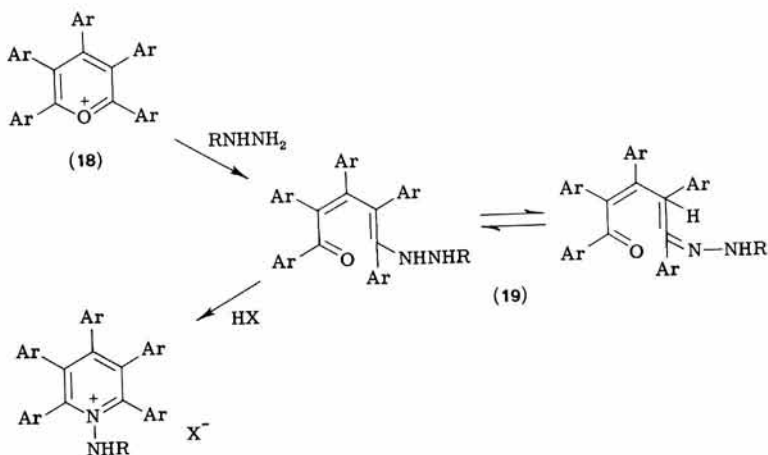
³¹ Y. Tamura and N. Tsujimoto, *Chem. Ind. (London)*, 926 (1970).

³² Y. Tamura, N. Tsujimoto, and M. Mano, *Chem. Pharm. Bull.* **19**, 130 (1971).



Hydrazine derivatives also open the ring of pyrylium salts (18) to form open-chain products (19) which undergo recyclization. The applicability of this method of synthesis is strictly limited as only polyaryl pyrylium salts react smoothly. Of possible hydrazine derivatives, only alkyl or aryl hydrazines were used.³³⁻⁴¹

Lempert *et al.*⁴² described the reaction of benzenesulfonyl hydrazide with pyrylium salts to give pyrazolins which on heating with perchloric acid are converted into 1-benzenesulfonylamino pyridinium salts.



³³ W. Schneider and F. Seebach, *Chem. Ber.* **54**, 2285 (1921).

³⁴ W. Schneider, *Ann.* **438**, 115 (1924).

³⁵ W. Schneider and W. Müller, *Ann.* **438**, 147 (1924).

³⁶ W. Schneider and W. Riedel, *Chem. Ber.* **74**, 1252 (1941).

³⁷ W. Schneider and K. Weiss, *Chem. Ber.* **61**, 2445 (1928).

³⁸ K. Dimroth, G. Arnoldy, S. von Eicken, and G. Schiffer, *Ann.* **604**, 221 (1957).

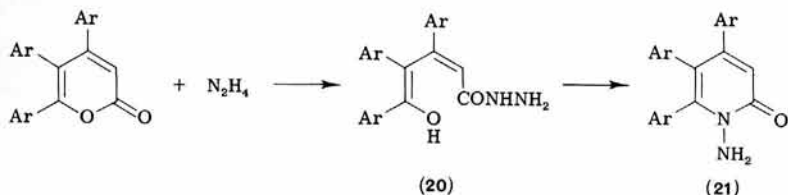
³⁹ A. T. Balaban, P. T. Frangopol, G. Mateescu, and C. D. Nenitzescu, *Bull. Soc. Chim. Fr.*, 298 (1962).

⁴⁰ A. T. Balaban, *Tetrahedron* **24**, 5059 (1968).

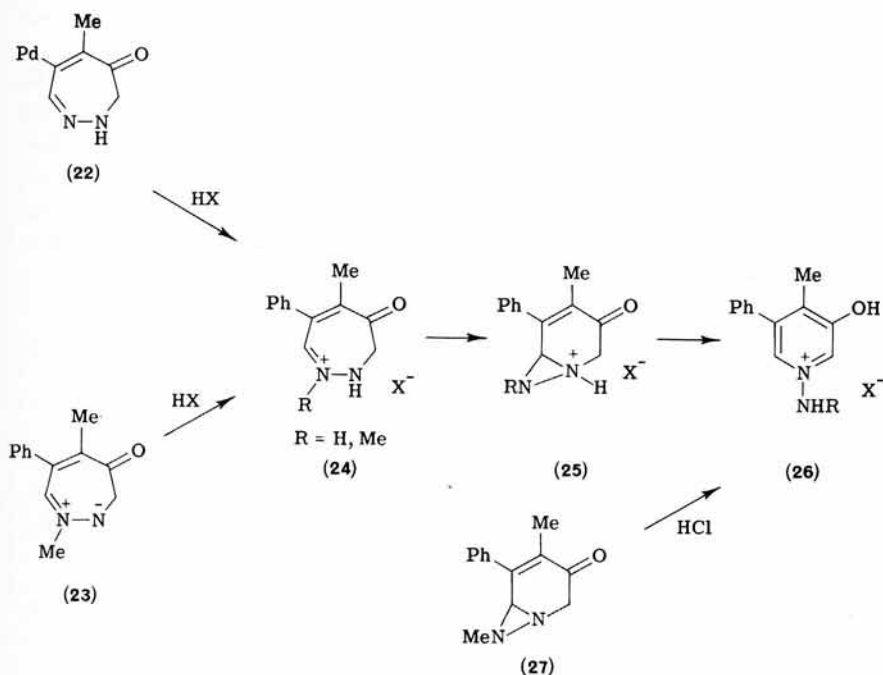
⁴¹ C. L. Pedersen, N. Harrit, and O. Buchardt, *Acta Chem. Scand.* **24**, 3435 (1970).

⁴² K. Lempert, *Acta Chim. Sci. Hung.* **65**, 443 (1970).

Analogous to the pyrylium salts, α -pyrones are also ring-opened by hydrazine derivatives.^{42a,43} Recyclization of the products (20) leads to *N*-aminopyridones (21).



N-Aminopyridinium salts (14), and their derivatives substituted at the exocyclic amino group, can also be prepared by rearrangement reactions. Thus, the diazepinone 22 and diazepinium betaine 23 are converted into the *N*-amino salts (26) by concentrated acids.⁴⁴⁻⁴⁷ This rearrangement



^{42a} I. El-S. El-Kholy, F. K. Rafla, and G. Soliman, *J. Chem. Soc.*, 4490 (1961).

⁴³ I. El-S. El-Kholy and F. K. Rafla, *J. Chem. Soc. C*, 974 (1969).

⁴⁴ J. A. Moore, *J. Amer. Chem. Soc.* **77**, 3417 (1955).

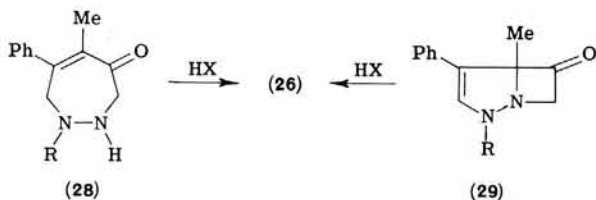
⁴⁵ J. A. Moore and J. Binkert, *J. Amer. Chem. Soc.* **81**, 6029 (1959).

⁴⁶ J. A. Moore, *Trans. N. Y. Acad. Sci.* **27**, 591 (1965).

⁴⁷ J. A. Moore and G. Pleiss, *J. Amer. Chem. Soc.* **90**, 4738 (1968).

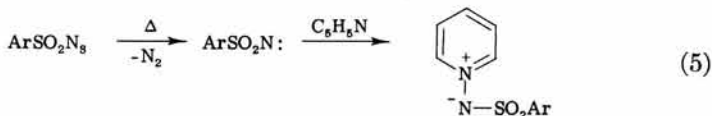
involves initial formation of the cation **24**, which gives the quaternary salt **26** via the bicyclic system **25** (see Section III,A,3). This mechanism is supported by the fact that the bicyclo[4,1,0] ketone **27** rearranges very rapidly in methanolic HCl to the *N*-methylaminopyridinium chloride (**26**; R = Me, X = Cl).⁴⁷

Under similar conditions 7-methoxy-1-acyl-1,2,3,7-tetrahydrodiazepin-4-one (**28**), the corresponding 1-tosyl compound, and the bicyclic ketones (**29**) also yield the quaternary salts (**26**).^{48,49}



2. Preparation from Azides and Pyridines

Nitrenes undergo addition reactions to neutral nucleophiles.^{50,51} Accordingly, they add to the nitrogen atom of pyridines, forming *N*-imines. This method of preparation was described first by Curtius *et al.*⁵²⁻⁵⁵ They heated aromatic sulfonyl azides in pyridine and obtained various *N*-sulfonylimines [Eq. (5)] the structures of which were not at that time recognized. They formulated sulfonyl nitrenes as intermediates in this reaction.



Since then, the thermolysis or photolysis of azides in the presence of pyridines has been developed into a widely applicable synthesis of *N*-imines, albeit in most cases in small yields (5–30%). Numerous sulfonyl

⁴⁸ J. A. Moore, F. J. Marascia, R. W. Medeiros, and R. L. Wineholt, *J. Org. Chem.* **31**, 34 (1966).

⁴⁹ J. A. Moore, E. V. Volker, and C. M. Kopay, *J. Org. Chem.* **36**, 2676 (1971).

⁵⁰ W. Lwowski, "Nitrenes." Wiley (Intersciences), New York, 1970.

⁵¹ S. Hünig, *Helv. Chim. Acta* **54**, 1721 (1971).

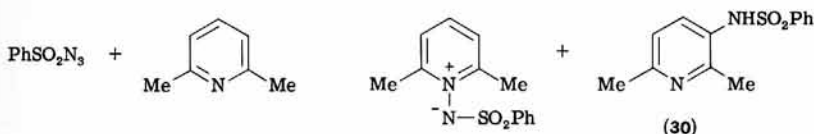
⁵² T. Curtius and J. Rissom, *J. Prakt. Chem.* [2] **125**, 311 (1930).

⁵³ T. Curtius and G. Kraemer, *J. Prakt. Chem.* [2] **125**, 323 (1930).

⁵⁴ T. Curtius and K. Vorbach, *J. Prakt. Chem.* [2] **125**, 340 (1930).

⁵⁵ T. Curtius and H. Bottler, *J. Prakt. Chem.* [2] **125**, 380 (1930).

azides,^{10,56-61} acyl azides,^{19,59,61} and cyano azides^{62,63} can be used as generators of nitrene. It has since been proved unequivocally that the formation of the *N*-imines according to Eq. (5) does involve nitrenes. Abramovitch and Takaya⁶⁴ isolated 3-benzenesulfonamido-2,6-lutidine (**30**) on thermolysis of benzenesulfonyl azide in 2,6-lutidine. This indicates the occurrence of free benzenesulfonyl nitrene.



3. Preparation by Rearrangement Reactions

Pyridine *N*-imines are stabilized by mesomerism (see Section III,A). Less stable compounds often rearrange to pyridine *N*-imines, as already discussed in Section II,A,1.

Further compounds capable of rearrangement are the diazepines **31**, **32**,⁶⁵ **34**, **35** and **36** and the bicyclic derivatives **37-39**.⁶⁶ At 170° they give pyridine *N*-imines in 60-80% yield, except for the diazepines **32** and **34**. Varying amounts of substituted pyridines are also isolated as thermolysis products, generated from the *N*-imines by cleavage of the N-N bonds (see Section IV,C).

The valence tautomeric diaziridines **33** are formulated as intermediates in these rearrangement reactions. At normal temperatures, the equilibrium diazepine \rightleftharpoons diaziridine is exclusively on the side of the diazepine. Thermal rearrangement of pyridine *N*-imines to diaziridines or diazepines has not yet succeeded;⁶⁷ such reactions are accessible by irradiation (see Section IV,F). These reactions are not controlled exclusively by orbital symmetry. The Hoffmann-Woodward rules⁶⁸ allow both thermal and photochemical

⁵⁶ J. N. Ashley, G. L. Buchanan, and A. P. T. Easson, *J. Chem. Soc.*, 60 (1947).

⁵⁷ G. L. Buchanan and R. M. Levine, *J. Chem. Soc.*, 2248 (1950).

⁵⁸ K. Hafner, D. Zinser, and K.-L. Moritz, *Tetrahedron Lett.*, 1733 (1964).

⁵⁹ P. K. Datta, *J. Indian Chem. Soc.* **24**, 109 (1947).

⁶⁰ R. A. Abramovitch and B. A. Davis, *Chem. Rev.* **64**, 149 (1964).

⁶¹ T. J. Prosser, A. F. Marcantonio, and D. S. Breslow, *Tetrahedron Lett.*, 2779 (1964).

⁶² F. D. Marsh, U. S. Patent 3,624,256 1971.

⁶³ Cited in ⁶⁰ Lwowski, p. 279.

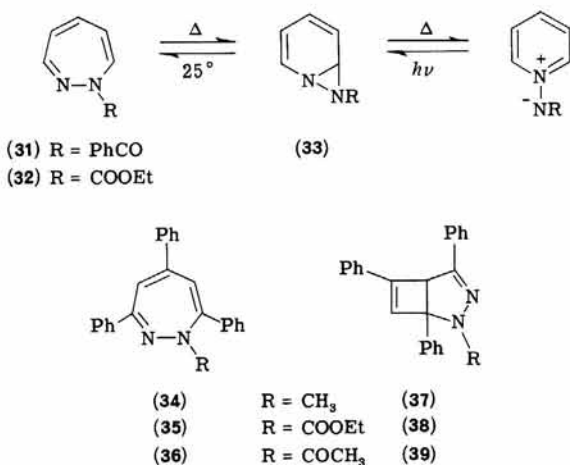
⁶⁴ R. A. Abramovitch and T. Takaya, *J. Org. Chem.* **37**, 2022 (1972).

⁶⁵ J. Streith and J.-M. Cassal, *Bull. Soc. Chim. Fr.*, 2175 (1969).

⁶⁶ G. Kan, M. T. Thomas, and V. Snieckus, *J. Chem. Soc. D.*, 1022 (1971).

⁶⁷ J. Streith, J. P. Luttringer, and M. Nastasi, *J. Org. Chem.* **36**, 2962 (1971).

⁶⁸ R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.* **1**, 17 (1968).

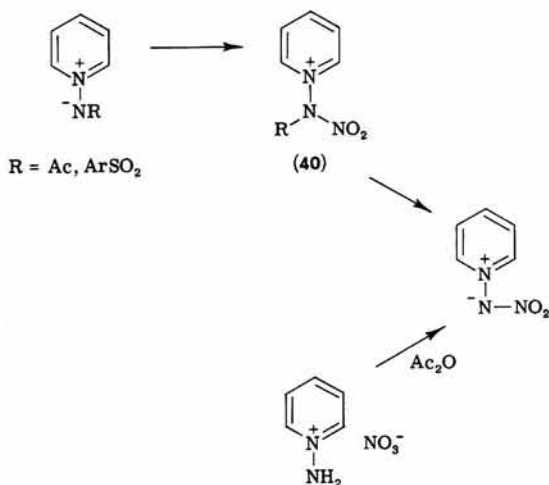


intramolecular cyclization and opening of the three-membered rings, and hence thermodynamic parameters decide the reaction direction.

4. Preparation from Other *N*-imines

The imino group of the *N*-imines is a nucleophilic reaction center (see Section IV,A). Some of the substitution reactions at this reaction center lead to other *N*-imines.

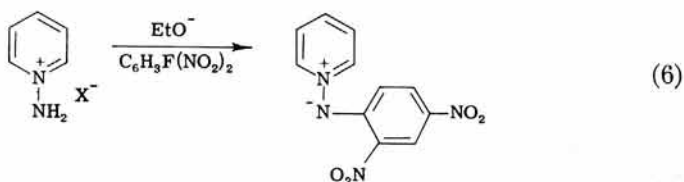
In this way, pyridine *N*-sulfonyl- and *N*-acylimines can be nitrated at the imino group in acetic acid-acetic anhydride.¹⁷ Intermediates of type



Scheme 1

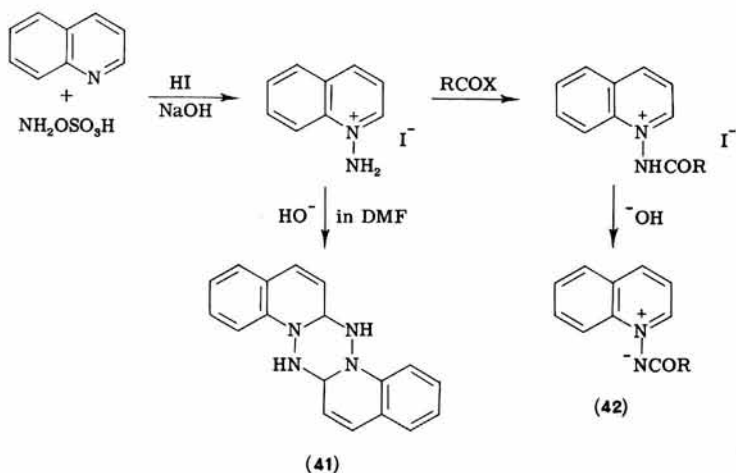
40 are formed from which the sulfonyl or acyl group is cleaved to yield pyridine *N*-nitroimines. The same products are also formed from *N*-amino-pyridinium nitrates and acetic anhydride⁶⁹ (Scheme 1).

With pyridine *N*-imine, 2,4-dinitrofluorobenzene gives pyridine *N*-2,4-dinitrophenylimine.^{70,71} Other polynitro aromatics react analogously. Since it is not possible to isolate the pyridine *N*-imine it is prepared *in situ* from *N*-aminopyridinium salts and sodium ethoxide [Eq. (6)].



B. QUINOLINE *N*-IMINES

Few quinoline *N*-imines have been synthesized, and these exclusively by the deprotonation of *N*-aminoquinolinium salts which can be obtained from hydroxylamine-*O*-sulfonic acid and quinoline.⁷² These salts can be



⁶⁹ J. Epsztajn and A. R. Katritzky, *Tetrahedron Lett.*, 4739 (1969).

⁷⁰ T. Okamoto, H. Horikiri, S. Hayashi, and M. Hirobe, *Yakugaku Zasshi* **91**, 210 (1971); *Chem. Abstr.* **74**, 99818k (1971).

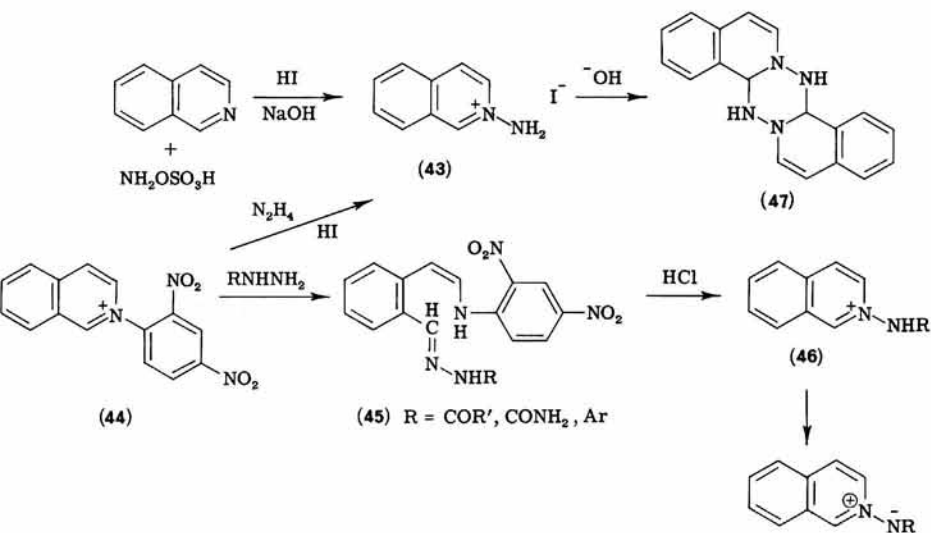
⁷¹ T. Okamoto, H. Horikiri, S. Hayashi, and M. Hirobe, *Yakugaku Zasshi* **91**, 216 (1971); *Chem. Abstr.* **74**, 99819m (1971).

⁷² T. Okamoto, M. Hirobe, and T. Yamazaki, *Chem. Pharm. Bull.* **14**, 512 (1966).

acylated^{72,73} and sulfonated⁷⁴ at the amino group. Deprotonation of *N*-acylamino and *N*-sulfonylamino salts by aqueous alkali gives stable quinoline *N*-imines,⁴² but the simple salts give only the hexahydrotetrazine derivatives (41),⁷² derived by dimerization of intermediate unsubstituted quinoline *N*-imines (see Section IV,E).

C. ISOQUINOLINE *N*-IMINES

Isoquinoline *N*-imines also have been made only by deprotonation of *N*-aminoisoquinolinium salts. Just as for the corresponding pyridinium derivatives (see Section II,A,1), the salts 43 can be produced by amination of isoquinoline with hydroxylamine-*O*-sulfonic acid⁷⁵ or from *N*-(2,4-dinitrophenyl) isoquinolinium chloride (44).^{30,31,76,77} Substituted quaternary amino salts (46) are obtained by cyclization of 2-(2,4-dinitroanilino)-*o*-styrylaldehyde hydrazones (45) with ethanolic hydrochloric acid, and deprotonation to *N*-imines is easily effected by alkali. On liberation from the salts by alkali, unsubstituted isoquinoline *N*-imines dimerize to give



Scheme 2

⁷³ Y. Tamura, H. Ishibashi, N. Tsujimoto, and M. Ikeda, *Chem. Pharm. Bull.* **19**, 1285 (1971).

⁷⁴ T. Shiba, K. Yamane, and H. Kato, *J. Chem. Soc. D*, 1592 (1970).

⁷⁵ R. Huisgen, R. Grashey, and R. Krischke, *Tetrahedron Lett.*, 387 (1962).

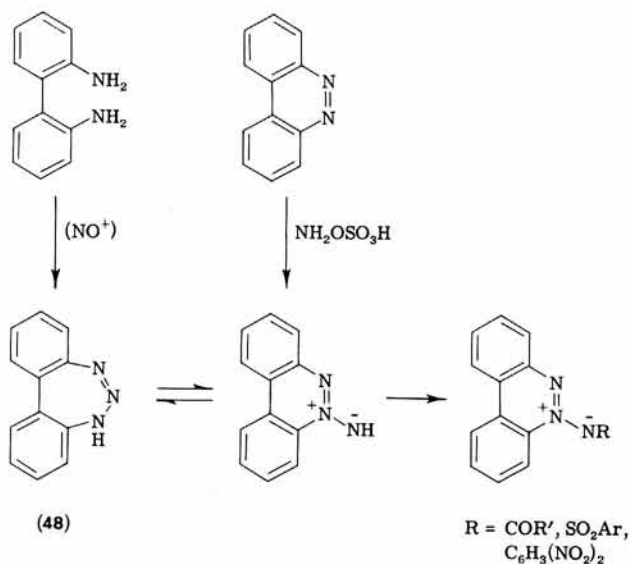
⁷⁶ Y. Tamura, N. Tsujimoto, and M. Uchimura, *Chem. Pharm. Bull.* **19**, 143 (1971).

⁷⁷ T. Zincke and G. Weissfenning, *Ann.* **396**, 103 (1913).

the hexahydrotetrazine derivatives **47**,^{75,76} from which it can be recovered by heating.

D. BENZOCINNOLINE *N*-IMINES

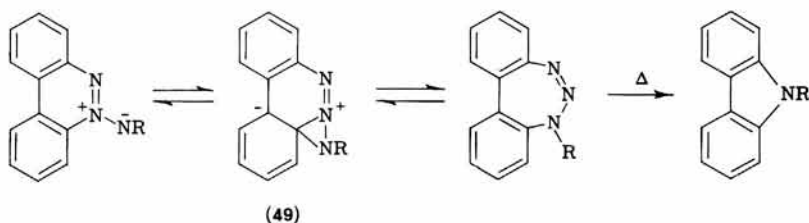
Two syntheses of benzocinnoline *N*-imines have been described recently.⁷⁸ They can be prepared from benzocinnoline and hydroxylamine-*O*-sulfonic acid or by diazotization of 2,2'-diaminobiphenyl with pentyl nitrite or *N*-nitrosodiphenylamine. Diazotization of the diamine presumably proceeds via the triazepine **48**, which is isomeric with unsubstituted benzocinnoline *N*-imine. Benzocinnoline *N*-imine itself, the only unsubstituted *N*-imine so far isolated, was prepared from benzocinnoline and hydroxylamine-*O*-sulfonic acid. Under similar conditions, quaternary *N*-amino salts were isolated from the other *N*-heterocycles. The unsubstituted *N*-imine can be converted easily into the acyl, sulfonyl, and 2,4-dinitrophenyl derivatives (Scheme 3).



Scheme 3

By analogy with the pyridine *N*-imines (Section II,A,3) the intermediate **49** can be assumed for the valence tautomerization *N*-imine \rightleftharpoons triazene. The equilibria of Scheme 4 are demonstrated by the formation of carbazoles in the thermal decomposition of benzocinnoline *N*-imines.

⁷⁸ S. F. Gait, C. W. Rees, and R. C. Storr, *J. Chem. Soc. D.*, 1545 (1971).



Scheme 4

E. 1,2,4-TRIAZOLE *N*-IMINES

The *N*-imines of *s*-triazoles have been investigated the most thoroughly of all the heterocyclic five-membered rings. All 1,2,4-triazole-*N*-imines prepared contain the *N*-imino group in the 4-position of the triazole ring.

4-Amino-1,2,4-triazoles (50) or their derivatives are usually starting material for the synthesis. They are readily available and already contain the exocyclic N-N bond required for heteroaromatic *N*-imines. 4-Amino-1,2,4-triazoles can be quaternized by alkyl halides or tosylates at the N-1 atom to give the salt 52.⁷⁹⁻⁸² (Scheme 5) The orientation of quaternization is proved by the reactions in Scheme 6 for the example of the quaternary acylamino salts 52. Quaternary salts of the type 52 can also be prepared by reaction of 1,3,4-oxadiazolium salts (51)⁸³ with aryl hydrazines⁸⁴ and from aryl hydrazine hydrohalides and orthoesters.⁸⁵ With alkali, the 1-alkyl-*s*-triazole-4-imines^{80-82,86} can be obtained in the normal manner from these salts (Scheme 5). The free *N*-imines are all stable except the *N*-unsubstituted compound itself.⁸⁷ Recently, other structures were tentatively reported⁸⁸ for the deprotonation products of analogous quaternary salts (52) with hydrazine.

⁷⁹ H. G. O. Becker, H. Böttcher, T. Röthling, and H.-J. Timpe, *Wiss. Z. Tech. Hochschule Chem. "Carl Schorlemmer" Leuna-Merseburg* **8**, 22 (1966).

⁸⁰ H. G. O. Becker, N. Sauder, and H.-J. Timpe, *J. Prakt. Chem.* **311**, 897 (1969).

⁸¹ H. G. O. Becker and H.-J. Timpe, *J. Prakt. Chem.* **312**, 1112 (1970).

⁸² H. G. O. Becker, K. Heimbürger, and H.-J. Timpe, *J. Prakt. Chem.* **313**, 795 (1971).

⁸³ G. V. Boyd and S. R. Dando, *J. Chem. Soc. C*, 1397 (1970).

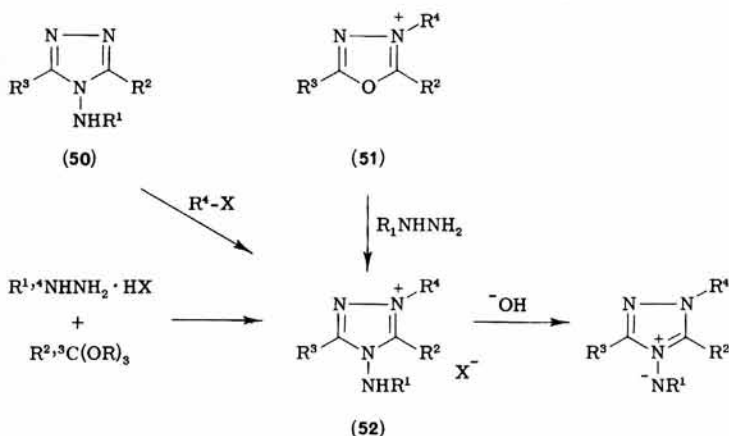
⁸⁴ G. V. Boyd and A. J. H. Summers, *J. Chem. Soc. C*, 409 (1971).

⁸⁵ C. Runti and C. Nisi, *J. Med. Chem.* **7**, 814 (1964).

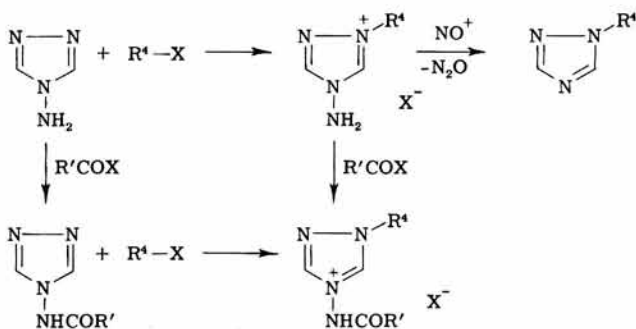
⁸⁶ G. V. Boyd and A. J. H. Summers, *J. Chem. Soc. B*, 1648 (1971).

⁸⁷ H.-J. Timpe, unpublished results, see Promotion-B-Thesis, TH Chemie, Merseburg, 1972.

⁸⁸ O. P. Shvaika and W. I. Fomenko, *Dokl. Akad. Nauk SSSR* **200**, 134 (1971).

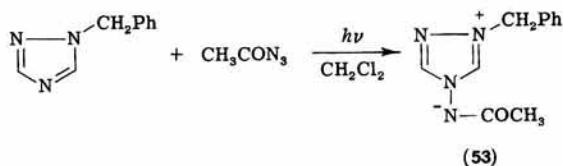


Scheme 5



Scheme 6

1-Alkyl-1,2,4-triazole 4-imines can be also prepared from azides and 1-alkyl-1,2,4-triazoles.⁸⁷ For instance, the *N*-imine **53** is produced when acetyl azide, which under these conditions gives acetyl nitrene,⁸⁹ is irradiated in the presence of 1-benzyl-8-triazole.

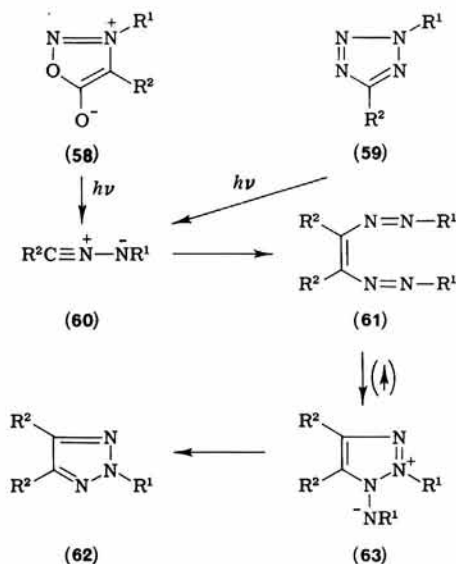


By analogy with the pyridine *N*-nitroimines (see Section II,A,4),

⁸⁹ R. Huisgen and J. P. Anselme, *Chem. Ber.* **98**, 2998 (1965).

(54) and alkali cyanides or arylsulfonates, respectively. The reaction proceeds via the bis azo compounds **55** and **56**, which cyclize to form the more stable 1,2,3-triazole *N*-imines.⁹³

Other bis azo compounds give *v*-triazole *N*-imines as intermediates. Thus, photolysis of sydnone (**58**)⁹⁴⁻⁹⁷ and of 2,5-disubstituted tetrazoles^{98,99} gives *v*-triazoles (**62**). These reactions probably involve the primary formation of nitrilimines (**60**) which dimerize to the bis azoethylene derivatives (**61**) which in turn cyclize to form the *v*-triazole *N*-imines. These, under the reaction conditions, cleave at the exocyclic N-N bond (see Section IV,F).



This reaction mechanism is supported by the photolysis of the tetrazoles (**59**) in the presence of dipolarophiles, to yield products proving the occurrence of nitrilimines (**60**).^{100,101} Bis diazoethylene derivatives, which

⁹³ H. Bauer, G. R. Bedford, and A. R. Katritzky, *J. Chem. Soc.*, 751 (1964).

⁹⁴ A. Chinone, Y. Huseya, and M. Ohta, *Bull. Chem. Soc. Jap.* **43**, 2650 (1970).

⁹⁵ Y. Huseya, A. Chinone, and M. Ohta, *Bull. Chem. Soc. Jap.* **44**, 1667 (1971).

⁹⁶ M. Märky, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta* **54**, 1275 (1971).

⁹⁷ C. S. Angadiyavar and M. V. George, *J. Org. Chem.* **36**, 1589 (1971).

⁹⁸ R. R. Fraser, M. M. Gurudatta, and K. E. Haque, *J. Org. Chem.* **34**, 4118 (1969).

⁹⁹ R. Scheiner and J. F. Dinda, *Tetrahedron* **26**, 2619 (1970).

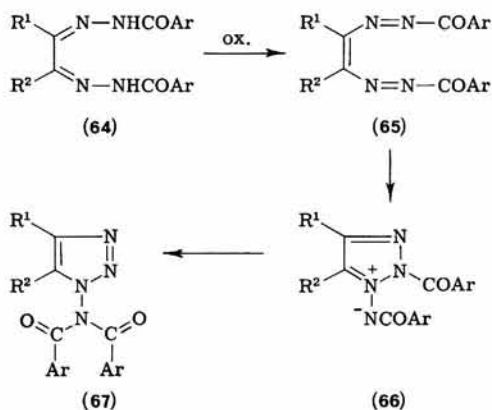
¹⁰⁰ P. Scheiner, *J. Org. Chem.* **34**, 199 (1960).

¹⁰¹ J. S. Clovis, A. Eckell, R. Huisgen, and R. Sustmann, *Chem. Ber.* **100**, 60 (1967).

are also available by oxidation of osazones,¹⁰²⁻¹⁰⁴ also lead to *v*-triazoles on photolysis.^{100,105,106} It is not clear whether the formation of *v*-triazoles **62** from the compounds **61** in sulfuric acid^{102,103} also proceeds via 1,2,3-triazole *N*-imines.

Recently¹⁰⁶ the *N*-imine structure (**63**) was even assigned to the bis azoethylene derivatives **61** on the basis of 1,3-dipolar cycloaddition reactions (see Section IV, E). Spectral evidence favors **61** as the predominant structure; however, an equilibrium could exist as shown $\mathbf{61} \rightleftharpoons \mathbf{63}$.

The oxidation of α -diketone bis acylhydrazones (**64**) yields initially bis azoethylene derivatives (**65**) which cyclize to give 1,2,3-triazole *N*-acylimines (**66**). It is now known that the final products of the oxidation reaction are not the compounds **66** but the isoimides, **67**. The structure of the products was the subject of some controversy: they were considered to be dihydrotetrazines¹⁰⁷⁻¹⁰⁹ and *N*-imines (**66**)^{110,111} but physical meth-



¹⁰² A. V. Spasov, D. Elenko, and S. Robev, *Bulg. Akad. Nauk, Otd. Geol.-Geogr. Khim. Nauk, Izv. Khim. Inst.* **1**, 217 (1951) [*Chem. Abstr.* **47**, 2153 (1953)]; **2**, 3 (1953) [*Chem. Abstr.* **49**, 5372 (1955)].

¹⁰³ R. B. Woodward and C. Wintner, *Tetrahedron Lett.*, 2697 (1969).

¹⁰⁴ J. Buckingham, *Quart. Rev. (London)* **23**, 37 (1969).

¹⁰⁵ C. Wintner, *Tetrahedron Lett.*, 2275 (1970).

¹⁰⁶ G. S. Angadiyavar, K. B. Sukumaran, and M. V. George, *Tetrahedron Lett.*, 633 (1971).

¹⁰⁷ H. v. Pechmann and W. Bauer, *Chem. Ber.* **33**, 645 (1900).

¹⁰⁸ H. v. Pechmann and W. Bauer, *Chem. Ber.* **42**, 664 (1909).

¹⁰⁹ R. Stollé, *Chem. Ber.* **59**, 1742 (1926).

¹¹⁰ S. Petersen and H. Heitzer, *Angew. Chem.* **82**, 81 (1970).

¹¹¹ A. R. Katritzky, referred to in Curtin and Alexandrou,¹¹³ and Alexandrou.¹¹⁴

ods,¹¹²⁻¹¹⁴ and especially X-ray analysis,¹¹⁵ recently proved the isoimide structure **67**. Evidently the *N*-acylimine **66**, as an azolide,¹¹⁶ acylated the exocyclic imino group to form the isoimide **67**. (see Section IV,C.)

G. THIAZOLE *N*-IMINES

Only one thiazole *N*-imine has been described without any description of its preparation.⁷⁴

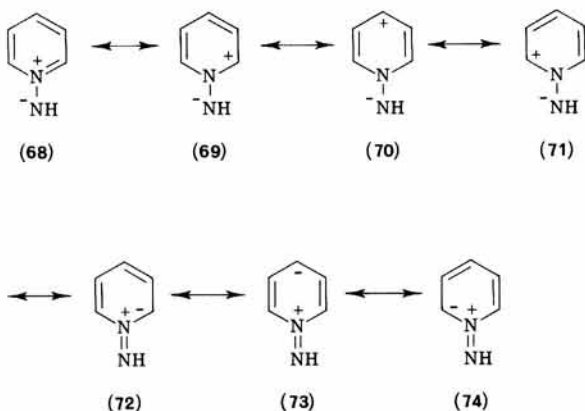
III. Physicochemical Properties

Systematic investigation of the physicochemical properties of heteroaromatic *N*-imines has been very limited. Available data are mostly hidden in the experimental sections of publications. The results of physicochemical investigations of *N*-imines discussed below are classified by method.

A. ELECTRON DENSITY DISTRIBUTION

To anticipate the results to be expected by physicochemical investigations, we shall discuss briefly the electron density distribution in the *N*-imines using valence bond language.

The prototype for an *N*-imine six-membered ring is the unsubstituted pyridine *N*-imine and has the mesomeric canonical forms **68-74**.



¹¹² N. E. Alexandrou and E. D. Micromastoras, *Tetrahedron Lett.*, 231 (1968).

¹¹³ D. Y. Curtin and N. E. Alexandrou, *Tetrahedron* **19**, 1697 (1967).

¹¹⁴ N. E. Alexandrou, *Tetrahedron* **22**, 1309 (1966).

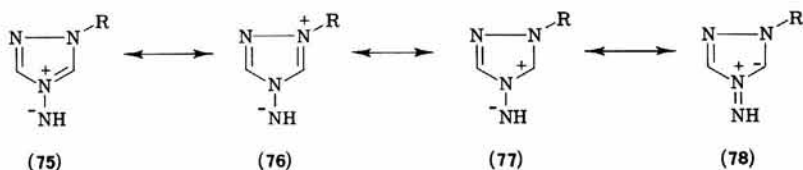
¹¹⁵ H. Bauer, A. J. Boulton, W. Fedeli, A. R. Katritzky, A. Majid-Hamid, F. Mazza, and A. Vaciago, *Angew. Chem.* **83**, 115 (1971).

¹¹⁶ H. A. Staab, *Angew. Chem.* **74**, 407 (1962); *Angew. Chem. Int. Ed. Engl.* **1**, 351 (1962).

Structures **68–71** indicate the possibility of delocalization of the positive charge in the heterocyclic ring, whereas the structure **72–74** show the possible interactions between the ring and the negative charge. It depends strongly on the substituent which of the structures **68–74** are the main contributors to the ground state of the pyridine *N*-imine.

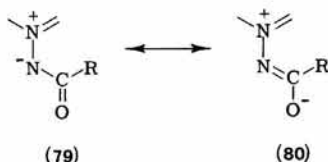
The mesomeric structures demonstrate that the 3- and 5-positions differ from the 2-, 4-, and 6-positions in electron density distribution and that the valence electrons of the *N*-imine can be polarized easily.

1,2,4-Triazole 4-imine, as a representative five-membered ring *N*-imine, possesses canonical forms **75–78** (excluding quadrupolar structures).



From these structures we deduce that the distribution of charge differs from that in pyridine *N*-imine: in the five-membered ring the positive charge cannot be delocalized over the whole ring, which causes a bigger difference between the electron density of the carbon-atoms.

In *N*-substituted *N*-imines, the negative charge can often be delocalized in the exocyclic substituent. This can be shown by the example of an *N*-acylimine by means of the mesomeric structures **79** and **80**. The case is analogous to other *N*-substituted *N*-imines. This possibility of delocalization is a significant difference between *N*-oxides and substituted *N*-imines.

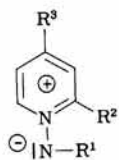


B. NMR INVESTIGATIONS

The differences of electron density discussed in Section III,A are especially visible in the NMR spectra of the *N*-imines.

Table I gives the proton signals of some pyridine *N*-imines. A clear difference in the chemical shift between H-2,6 and H-3,4,5 can be attributed partially to the different electron density at the carbon-atom in

TABLE I
NMR SPECTRA OF SOME PYRIDINE *N*-IMINES^a



R ¹	R ²	R ³	H-2, 6	H-3, 4, 5	Ref.
COOCH ₂ CH ₃	H	H	1.34 (6)	2.14–2.59	19
COOCH(CH ₃) ₂	H	H	1.14 (2 and 7)	2.34 (2 and 7)	67
COPh	H	H	1.07 (7)	1.77–2.67	19
SO ₂ C ₆ H ₇	H	H	1.40 (7)	1.92–2.45	19
COOCH ₂ CH ₃	H	CH ₃	1.54 (7)	2.60 (6)	19
COOCH ₂ CH ₃	H	Ph	1.28 (7, 5)	2.36 (7, 5)	67
COOCH ₂ CH ₃	H	N(CH ₃) ₂	1.84 (7, 5)	3.38 (7, 5)	19
COOCH ₂ CH ₃	H	COOCH ₂ CH ₃	1.05 (6)	1.97 (6)	19
COOCH ₂ CH ₃	H	<i>p</i> -ClC ₆ H ₄ CO	0.86 (7)	2.40 (7)	67
COOCH ₂ CH ₃	CH ₃	H	1.38	2.02–2.61	19

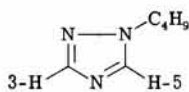
^a Measured in CDCl₃; τ scale; (in parentheses the coupling constants in Hz).

question. Unfortunately the exact position of H-4 cannot be read from the spectra, but, at any rate, it is less deshielded than H-2 and H-6. All chemical shifts are strongly influenced by the substituents; the change at H-2, 6 is attributed essentially to electronic effects.

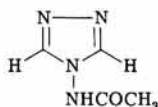
The NMR spectra also illustrate the isoelectronic character of *N*-oxides and *N*-imines, since the parent pyridine *N*-imine, stable only in solution, possesses the same NMR spectrum in D₂O as pyridine *N*-oxide.¹⁷

Apart from the pyridine *N*-imines,^{17, 19, 67, 70, 71} NMR spectra have been described only for the 1,2,4-triazole 4-imines.^{80–83, 87} The differences in electron density between C-3 and C-5 are reflected in the chemical shifts of the corresponding protons; see the NMR spectra of the *N*-imine **84**⁸⁷ (Scheme 7). The difference between the values for H-3 and H-5 is 1.1 ppm, the same as that of the quaternary acylamino salt **83**.

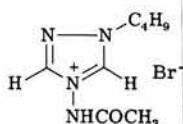
Because of the high electron density in the imino group (see canonical structures **79** and **80**), the protons of the substituents on the amino group are considerably shielded as can be observed in the NMR spectra of compounds (**82–84**).



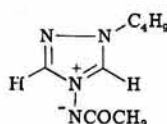
(81)



(82)



(83)



(84)

Chemical Shifts (τ values)

	(81)	(82)	(83)	(84)
H-3	1.4	1.4	0.9	1.5
H-5	1.9	1.4	-0.2	0.4
CH ₃	—	7.8	7.7	8.1

Scheme 7

The NMR spectra also allow qualitative conclusions regarding the electronic effect of the imino group. However, caution is needed since chemical shifts are dependent on numerous other factors. A comparison of the position of the signals in *N*-imine **84** and in the corresponding quaternary salt **83** (Scheme 7) shows that the protons of the *s*-triazole ring are less deshielded. The NMR signals are shifted to higher field by ~ 0.6 ppm as compared to those in the salt **83** with H-3 at even higher field than for the 1-alkyl-*s*-triazole (**81**). This shows the electron donor effect of the acylimino group.

Analogous evaluation of other substituted *s*-triazole 4-imine NMR spectra shows⁸⁷ that the carbamoylimino, the sulfonylimino, and the arylimino groups⁸⁶ act as donors, whereas the nitroimino group acts as an electron acceptor. From the NMR data, the arylimino group in pyridine *N*-imines is also an electron donor.^{70,71} (For quantitative constants of these substituents see Section III, C.)

C. IR INVESTIGATIONS

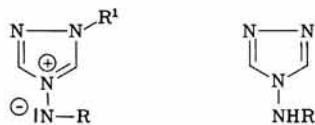
From canonical forms **79** and **80** it follows that for the multiple bonds within the imino group substituent the polarity rises and the bond order is reduced. Consequently, the force constants of such bonds are also reduced, causing a frequency shift to lower wavenumbers.^{117,118}

The frequency change is evident from the data for *s*-triazoles in Table II. The wavenumbers of the *N*-imine functional groups, except for the *N*-sulfonylimines, are shifted ~ 100 cm⁻¹ to lower values. The mean

¹¹⁷ H. A. Szymanski, "Theory and Practice of Infrared Spectroscopy." Plenum, New York, 1964.

¹¹⁸ W. Brögel, "Einführung in die Ultrarotspektroskopie." Steinkopff, Darmstadt, 1962.

TABLE II

IR FREQUENCIES OF 1,2,4-TRIAZOLE DERIVATIVES (CM⁻¹; MEASURED IN KBr)

R		Ref.		Ref.
COR ¹	1590	80	1700	87
CONHR ¹	1580	82	1700	87
SO ₂ Ar	1300	1150	1360	1175
NO ₂	1420	1300	1530	1315 ^a

^a Values for aromatic nitramines as the analogous *s*-triazole derivatives are unknown [P. Wetzel, *Chem. Ber.* **104**, 808 (1971)].

absorption frequencies listed in Table II are also typical for other heterocyclic *N*-imines. The absorption in *N*-acylimines is always found between 1570 and 1600 cm⁻¹,^{11,12,14,18,19,67,78} and that of *N*-nitroimines at 1420 and 1300 cm⁻¹.^{17,69} These numbers suggest a considerable mesomeric stabilization of negative charge in the imino group. The conditions are analogous in the *N*-cyanoimines, the nitrile vibration occurring in the range 2130–2150 cm⁻¹,⁹³ which is similar to that for cyanamide anions (2110 cm⁻¹).

In pyridine *N*-nitroimines, the resonance interaction between the nitroimino group and the pyridine ring was investigated by IR spectroscopy. A σ_R^0 value of (+ or -) 0.25 was found by means of integrated intensities (for the method see Brownlee *et al.*¹¹⁹) which is of the same order of magnitude as that of the N⁺-O⁻ group in pyridine *N*-oxide (-0.21).¹²⁰ The sign is probably negative, i.e., the nitroimino group behaves as a resonance donor. See also Section III,B.

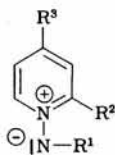
D. UV INVESTIGATIONS

The valence electrons in *N*-imines can be polarized easily (see Section III,A). Accordingly, the *N*-imines possess relatively long wavelength UV transitions which are shifted bathochromically as compared to the absorption of the parent heterocycles.

¹¹⁹ R. T. Brownlee, R. E. J. Hutchinson, A. R. Katritzky, T. T. Tidwell, and R. D. Topsom, *J. Amer. Chem. Soc.* **90**, 1757 (1968).

¹²⁰ A. R. Katritzky, C. R. Palmer, F. J. Swinbourne, T. T. Tidwell, and R. D. Topsom, *J. Amer. Chem. Soc.* **91**, 636 (1969).

TABLE III
UV DATA FOR SOME PYRIDINE *N*-IMINES



R ¹	R ²	R ³	Solvent	λ_{max} (ϵ)		Ref.
H	H	H	H ₂ O	322 (10,000)		17
COOCH ₂ CH ₃	H	H	MeOH	228 (6600)	315 (5530)	19
COOCH(CH ₃) ₂	H	H	C ₆ H ₆	282 (2900)	344 (11,600)	67
COPh	H	H	MeOH	233 (13,530)	317 (4850)	19
SO ₂ C ₇ H ₇	H	H	MeOH	240 (14,000)	317 (2180)	19
COOCH ₂ CH ₃	H	CH ₃	MeOH	230 (5490)	245 (5880)	19
				312 (4620)		
COOCH ₂ CH ₃	H	CH ₃	C ₆ H ₆	341 (9400)		67
COOCH ₂ CH ₃	H	Ph	C ₆ H ₆	370 (19,000)		67
COOCH ₂ CH ₃	H	N(CH ₃) ₂	MeOH	298 (23,460)		19
COOCH ₂ CH ₃	H	COOCH ₂ CH ₃	MeOH	231 (6460)	274 (4340)	19
				350 (9900)		
COOCH ₂ CH ₃	H	<i>p</i> -ClC ₆ H ₄ CO	C ₆ H ₆	395 (17,900)		67
COOCH ₂ CH ₃	CH ₃	H	MeOH	242 (5300)	277 (3350)	19
				310 (2050)		
COOCH ₂ CH ₃	CN	H	MeOH	224 (11,000)	246 (7850)	
				360 (4300)		65
COCH ₃	CH ₃	H	C ₆ H ₆	336 (5600)		67

Typical UV spectra of some pyridine *N*-imines are summarized in Table III. The spectra of the *N*-imines unsubstituted in the heterocyclic ring contain two transitions near 230 and 320 nm¹⁸ which are strongly dependent on the solvent. In addition, ring-substituted compounds show absorption at ~ 270 nm. In the same solvent, the position of the absorption bands is only slightly dependent on the substituent of the imino group, with the exception of the *N*-arylimines.^{38,70,71} The azomethine imine system of the *N*-imines is apparently the essential chromophore since these compounds show analogous absorption frequencies (for a summary of azomethine imines see Timpe.¹²¹)

From the high extinction values and the Pariser-Parr-Pople model

¹²¹ H.-J. Timpe, *Wiss. Z. Tech. Hochschule Chem. "Carl Schorlemmer" Leuna-Merseburg* **14**, 102 (1972).

calculations¹²² it follows that the long-wave absorptions of the pyridine *N*-imines are π - π^* transitions. Charge is transferred by excitation from the imino group to the ring and a lowering of the bond order occurs simultaneously.

N-imines of five-membered heterocycles also possess relatively long wavelength transitions compared with those of the parent heterocycles.^{74, 80, 82, 87, 93} Thus, in protic solvents the absorption maxima for 1,2,4-triazole 4-imines are situated at ~ 250 nm, whereas the corresponding triazoles absorb at ~ 210 nm.

The dipolar character of *N*-imines renders the UV transitions strongly solvent-dependent. For all compounds investigated hitherto the long-wavelength absorption band possesses a negative solvatochromism (see Table III and Dimroth *et al.*³⁸ and Becker *et al.*⁸²). The molar transition energies of pyridine *N*-arylimines^{38, 123} and 1,2,4-triazole 4-imines,^{82, 124} derived from the absorption frequencies, correlate well with the empirical solvent parameters E_T , Z , and S ; correlation with the parameters K , R , and δ (see Fowler *et al.*¹²⁵) are poor.

E. MASS SPECTROMETRY

Systematic investigations of the mass spectrometric fragmentation of heteroaromatic *N*-imines show a difference between the behavior of five- and six-membered ring compounds.

A direct investigation of unsubstituted *N*-imines by mass spectrometry is impossible since these compounds are stable only in solution. Unsubstituted pyridine *N*-imines are formed on heating *N*-aminopyridinium chlorides in the direct inlet system at 200°, as was shown by Tamura and co-workers.¹²⁶ The mass spectrum of the unsubstituted *N*-imines (see Scheme 8) contains peaks due to the loss of 15 (NH) and 16 (NH₂) mass units from the molecular ion in a ratio of $\sim 2.5:1$. HCN is also eliminated from the molecular ion to a small extent, the reaction presumably proceeding via the sequence molecular ion \rightarrow **85** \rightarrow **86**; see also thermal *N*-imine \rightleftharpoons diazepine tautomerism in Section II, A, 3.

The introduction of methyl substituents in the 2- and 6-positions of the pyridine ring changes significantly the intensity ratio of the peaks [M-NH]:[M-NH₂] in favor of the M-NH₂ fragmentation. This can be

¹²² R. Gleiter, D. Schmidt, and J. Streith, *Helv. Chim. Acta* **54**, 1645 (1971).

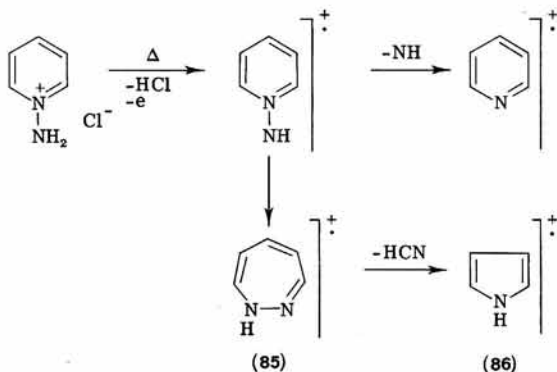
¹²³ Ch. Reichardt, and K. Dimroth, *Fortschr. Chem. Forsch.* **11**, 1 (1968).

¹²⁴ H. G. O. Becker and H.-J. Timpe, *Chimia* **26**, 473 (1972).

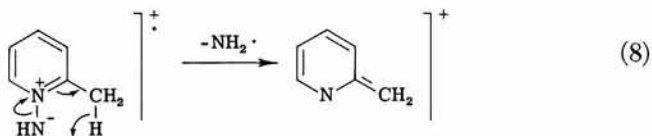
¹²⁵ F. W. Fowler, A. R. Katritzky, and R. J. D. Rutherford, *J. Chem. Soc. B*, 460 (1971).

¹²⁶ M. Ikeda, N. Tsujimoto, and Y. Tamura, *Org. Mass Spectrom.* **5**, 935 (1971).

explained by the so-called "ortho effect" [Eq. (8)]. Thus, the behavior of the pyridine *N*-imines is analogous to that of the *N*-oxides.¹²⁷



Scheme 8



Electron impact fragmentation of pyridine and isoquinoline *N*-acylimines¹²⁸ causes three primary cleavages: loss of an H atom, N-N bond cleavage, and cleavage α to the acyl group, (see Scheme 9). The cleavage of an H atom leads to a completely aromatized structure (87). Therefore, the $[M-1]$ ion is in most cases the base ion of the spectrum. Mass spectrometric investigations of deuterated compounds confirm the cleavage of the 2-H atom of the pyridine ring.

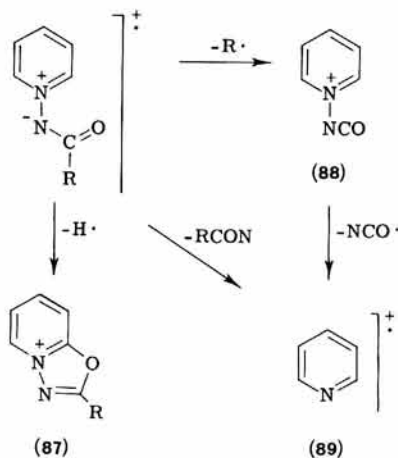
Cleavage α to the acyl group leads to the fragment ion **38** from which NCO is eliminated to give the pyridine radical ion **39**. The same ion is also produced directly by a one-step mechanism from the molecular ion. However, the possibility of the formation of the ion **39** by thermal decomposition cannot be excluded since no metastable ion was observed (see Section IV,E).

While not showing the $M-1$ cleavage, the mass spectra of the 1,2,4-triazole 4-acylimines¹²⁹ demonstrate the other two typical fragmentations.

¹²⁷ D. A. Lightner, R. Nicoletti, G. B. Qiustad, and E. Irwin, *Org. Mass Spectrom.* **4**, 571 (1970) and the references cited therein.

¹²⁸ M. Ikeda, N. Tsujimoto, and Y. Tamura, *Org. Mass Spectrom.* **5**, 61 (1971).

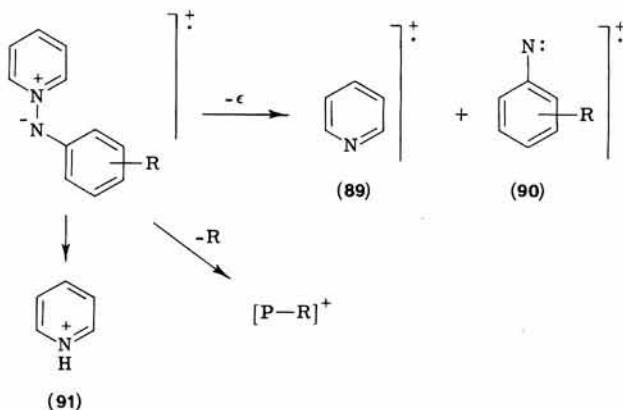
¹²⁹ H. G. O. Becker, D. Beyer, and H.-J. Timpe, *Z. Chem.* **10**, 264 (1970).



Scheme 9

Futhermore, the spectra of all pyridine and isoquinoline *N*-acylimines, and *s*-triazole 4-acylimines, contain a number of peaks of lower intensity which are determined essentially by the substituents.

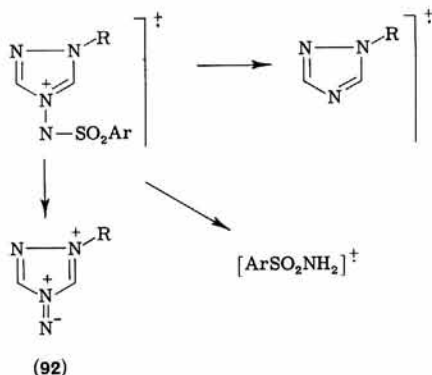
The mass spectroscopic fragmentation of pyridine and isoquinoline *N*-arylimines¹³⁰ is readily interpreted (see Scheme 10). The N-N bond cleavage is dominant, leading to the pyridine ion **89** and to ionized phenyl nitrene (**90**). The spectra also contain the fragment ion **91** derived directly from the molecular ion by hydrogen rearrangement. Chloro- and nitro-substituted *N*-arylimines ($R = \text{Cl}$ or NO_2) also show a fragment ion caused by loss of a chlorine atom or the nitro group.



Scheme 10

¹³⁰ M. Ikeda, N. Tsujimoto, and Y. Tamura, *Org. Mass Spectrom.* **5**, 389 (1971).

The primary fragmentation and rearrangement processes in the molecular ions of the *N*-sulfonylimines are more numerous. Scheme 11 shows the primary fragmentations of 1,2,4-triazole 4-sulfonylimines.⁸¹ The favored reaction is the cleavage of the N-N bond, as is shown clearly by spectra at low electron energy. Cleavage of the N-S bond is much less frequent, giving rise to **92**, which formally corresponds to an ionized 1,2,4-triazolium nitrene.



Scheme 11

The spectra of the *s*-triazole 4-sulfonylimines differ clearly from those of the pyridine *N*-sulfonylimines.¹³¹ These latter compounds possess the following four principal fragmentation processes: N-S bond cleavage, rearrangement reactions to ionized *N*-arylimines and azacarbazoles, the loss of hydrogen atom from the molecular ion, and the cleavage α to the SO_2 group.

Electron impact-induced fragmentations and photochemical reactions (see review, Bentley and Johnstone¹³²) of *N*-imines show but little similarity; analogous results are found only in the N-N bond cleavage.¹³³ The same applies to the thermal and mass spectrometric process.¹²⁸

F. ACID-BASE INVESTIGATIONS

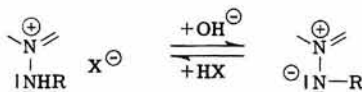
N-Imines are bases which can be protonated at the imine nitrogen atom to give *N*-aminoimmonium salts, Eq. (9). The $\text{p}K_a$ values for proton loss for different *N*-ammonium salts are given in Table IV. The difference between substituted *N*-imines derived from the same heterocycle can be

¹³¹ M. Ikeda, S. Kato, Y. Sumida, and Y. Tamura, *Org. Mass Spectrom.* **5**, 1383 (1971).

¹³² T. W. Bentley and R. A. Johnstone, *Advan. Phys. Organ. Chem.* **8**, 152 (1970).

¹³³ H.-J. Timpe and H. G. O. Becker, *J. Prakt. Chem.* **314**, 325 (1972).

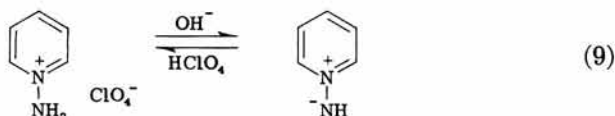
TABLE IV

p*K_a* VALUES OF VARIOUS *N*-IMINES (MEASURED IN WATER)

Nitrogen heterocycle	R	p <i>K_a</i> values	Ref.
Pyridine	H	11.2 ^a ; 13.6 ^b	10;17
Pyridine	CH ₃ CO	3.6 ^a	10
Pyridine	PhCO	3.2 ^a	17
Pyridine	NO ₂	-4.6 ^b	17
Pyridine	CH ₃	12-13 ^a	10
4-(1-Benzyl- <i>s</i> -triazole)	CH ₃ CO	4.5 ^a	87
4-(1- <i>n</i> -Butyl- <i>s</i> -triazole)	CH ₃ CO	4.9 ^a	87
3-Phenyl-4-methyl-5-hydroxypyridine	CH ₃ CO	4.2 ^a	22
3-Phenyl-4-methyl-5-hydroxypyridine	C ₂ H ₅ CO	4.1 ^a	22
3-Phenyl-4-methyl-5-hydroxypyridine	PhCO	3.3 ^{a,c}	22
3-Phenyl-4-methyl-5-hydroxypyridine	CF ₃ CO	2.4 ^{a,c}	22

^a Determined by potentiometric titration.^b Determined by spectroscopic method.^c Measured in 50% methanol.

explained qualitatively by the common effect of substituents. Further data needed for quantitative evaluation are lacking.

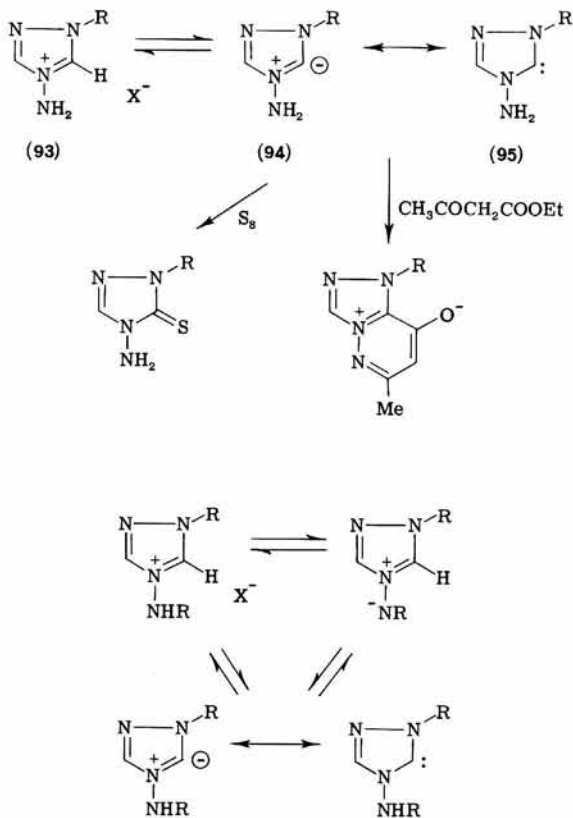


However, *N*-ammonium salts as well as the *N*-imines possess further acidic hydrogen atoms. In 0.2 *N* NaOD, *N*-aminopyridinium salts (**14**) exchanged their hydrogen atoms at the 2-, and 4-, and 6-positions for a D atom within the time the NMR spectra could be measured.¹⁷ For the 4-amino-*s*-triazolium salts (**93**) base catalysis is not needed for the hydrogen exchange.¹³⁴ The ylid or nucleophilic carbene structures **94** and **95** are intermediates (see also Wanzlick¹³⁵ and Quast and Hunig¹³⁶) and can be intercepted by sulfur or ethyl acetoacetate.¹³⁴

¹³⁴ H. G. O. Becker, D. Nagel, and H.-J. Timpe, *J. Prakt. Chem.* **315**, 97 (1973).¹³⁵ H. W. Wanzlick, *Angew. Chem.* **74**, 122 (1962).¹³⁶ H. Quast and S. Hünig, *Chem. Ber.* **99**, 2017 (1966).

Uncatalyzed H/D exchanges in D_2O are also observed in 1,2,4-triazole 4-imines^{80-82,86,87,90} and pyridine *N*-arylimines,¹³⁰ whereas other pyridine *N*-imines^{17,130} exchange only in the presence of bases.

These experimental results support the equilibria for *s*-triazole 4-imines of Scheme 12. Further evidence is the fact that the *N*-imines react with elemental sulfur without a catalyst^{82,87} (see also Section IV, C).



Scheme 12

IV. Chemical Properties

A. GENERAL DISCUSSION OF REACTION POSSIBILITIES

The heterocyclic *N*-imines possess five favored reaction centers (see Fig. 1): (a) the nucleophilic imino group, (b) acidic C-H atoms, (c)

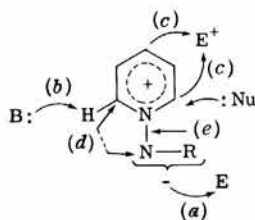


Fig. 1. Favored reaction centers of heterocyclic *N*-imines: (a) the nucleophilic imino group, (b) acidic C-H atoms, (c) electrophilic C atoms of the heterocyclic ring, (d) the dipolar azomethine imine structure, (e) the N-N bond which can be cleaved easily.

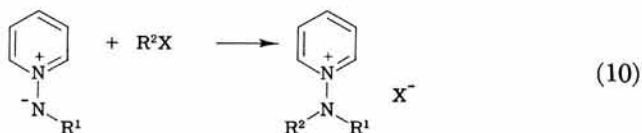
electrophilic or nucleophilic C atoms of the heterocyclic ring, (d) the dipolar azomethine imine structure, (e) the N-N bond which can be cleaved easily. In consequence of the dipolar character of the *N*-imines, intramolecular reactions are expected.

The known reactions are assigned to types (a)–(e) (Fig. 1), but the assignment is sometimes uncertain. Intramolecular and photochemical reactions are treated separately.

B. REACTIONS OF THE IMINO GROUP

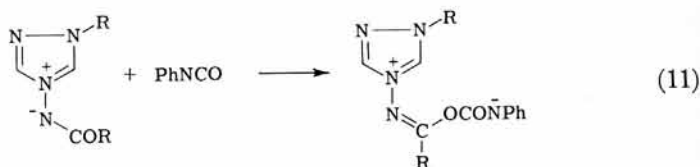
The nucleophilic imino group reacts as expected in protonation, alkylation, and acylation; for protonation processes see Section III,F.

Unlike some aliphatic amine *N*-imines,⁶ heteroaromatic *N*-imines are always alkylated at the nitrogen atom of the imino group,^{11,12,14,34,37,72,86,87} [Eq. (10)] although mesomerism also affords other points of attack (see Section III,A). The alkylation of unsubstituted pyridine *N*-imines with polynitrohalobenzenes yields *N*-(polynitroarylimines) (see Section II, A,4).



Acylation reactions with acid chlorides⁸⁶ also lead to *N*-substituted products. *N*-Acyl- and *N*-sulfonylimines react analogously in nitration reactions (see Section II, A,4).

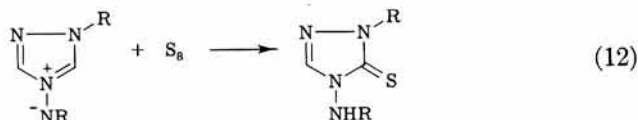
The reaction of 1,2,4-triazole 4-acylimines with phenyl isocyanate takes another course. In this case, dipolar compounds are formed by acylation at the oxygen atom of the imino group [Eq. (11)].



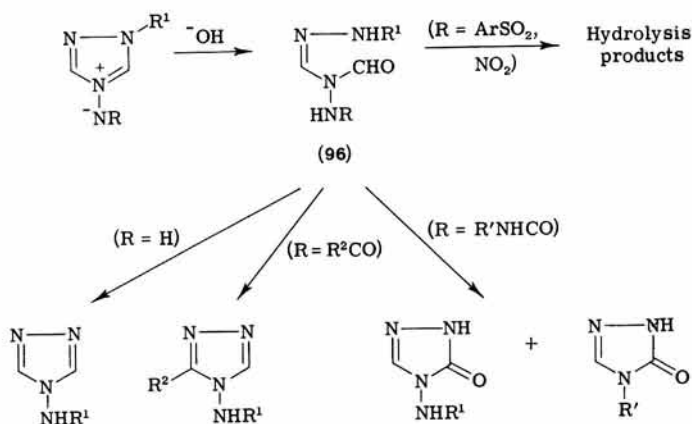
C. REACTIONS OF A RING CARBON AS AN ELECTROPHILE OR NUCLEOPHILE

C-H Bonds located near the quaternary ammonium group are acidic. Hydrogen atoms adjacent to the imino group are therefore easily exchanged in deuterated solvents (see Section III, F).

The C-H acidity is also the cause of the reaction of 1,2,4-triazole 4-imines with elemental sulfur [Eq. (12)]^{82,87} (see Section III, F). It is not clear whether this reaction is an electrophilic substitution or whether it proceeds via an intermediate ylid/carbene (94/95).



Heterocyclic *N*-imines contain a quaternary azomethine group which can be attacked by hydroxyl ions, leading to ring-opening. Such reactivity is strongly dependent on the heterocycle. For instance, pyridine *N*-imines are rather stable to bases^{17,69} whereas the 1,2,4-triazole 4-imines react very easily.^{80,82,90,137} In this reaction, the open-chain formamide **96** is

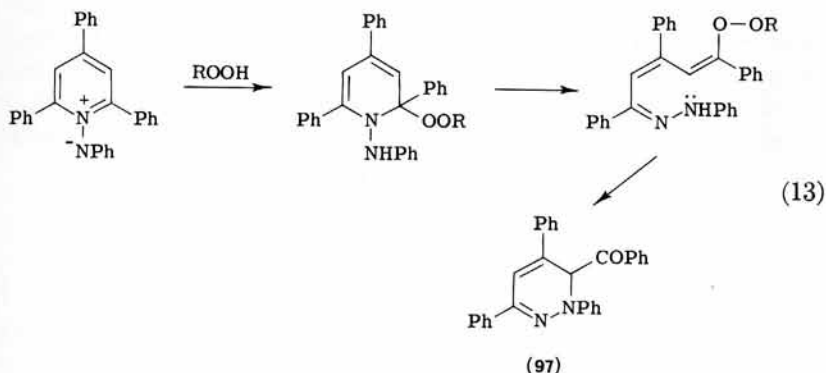


Scheme 13

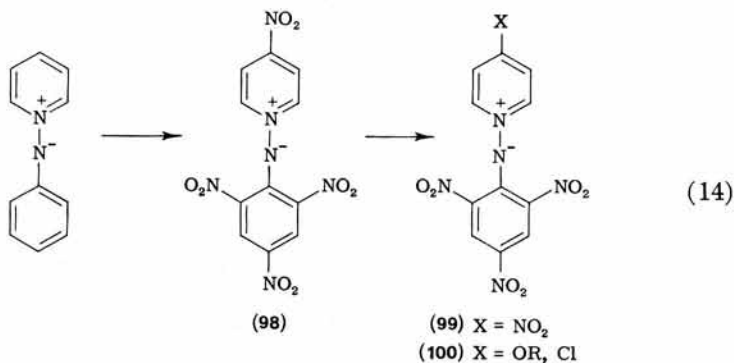
¹³⁷ H. G. O. Becker and H.-J. Timpe, *J. Prakt. Chem.* **311**, 9 (1969).

produced, which in alkaline solution gives one or the other of the compounds of Scheme 13, depending on the imino-group substituent.

Hydroperoxides (*t*-butyl hydroperoxide, cumyl hydroperoxide, and hydrogen peroxide) add to the azomethine bond of pyridine *N*-aryl-imines.¹³⁸ The primary addition product reacts as indicated in Eq. (13) and leads to 1,6-dihydropyridazine derivatives (97). Unsymmetrically substituted *N*-arylimines furnish two products; the structure of the hydroperoxide has no influence upon the nature of the final product.



The nitration of pyridine *N*-arylimines^{70,71} provides the only example of a ring carbon behaving as a nucleophile in being attacked by an electrophile. These compounds are nitrated to the trinitro derivative **98** prior to substitution in the heterocyclic ring. This reaction is so far the sole example of an electrophilic substitution at the heterocyclic ring of an *N*-imine. The nitro group in **99** can be exchanged for alkoxyl or chloro by RO^- and Cl^- ions (**100**) [Eq. (14)].

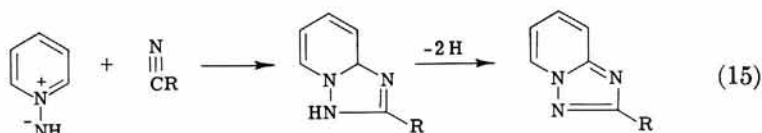


¹³⁸ V. Snieckus and G. Kan, *Tetrahedron Lett.*, 2267 (1970).

D. 1,3-DIPOLAR REACTIONS

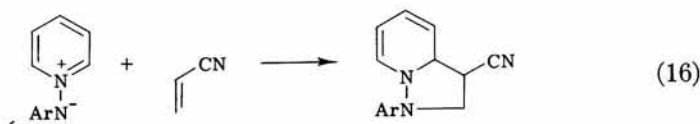
As previously pointed out, heteroaromatic *N*-imines contain the structural element of an azomethine imine. A typical reaction of this class of compound is 1,3-dipolar cycloaddition.^{121,139} In heteroaromatic *N*-imines, such reactions are difficult since they involve loss of the aromaticity of the heterocyclic ring. Factors essential to the success or failure of a 1,3-dipolar reaction are the aromatic character of the parent heterocycle, the electron effect of the substituent R, and the nature of the dipolarophile.

Unsubstituted pyridine, quinoline, and isoquinoline *N*-imines are the most reactive of all *N*-imines. They add to nitriles,^{10,13,72,140,141} acetylenedicarboxylic ester,^{75,139,142} propiolonitrile,¹⁴³ propiolic esters,¹⁴⁴ and carbon disulfide.¹³⁹ Dehydrogenation to a completely aromatic product, subsequent to the addition step [see Eq. (15)] exerts an essential influence on the course of the reaction.



Such rearomatization of the cycloaddition product in substituted *N*-imines is impossible without a considerable change of the molecular structure, and these compounds seldom undergo 1,3-dipolar cycloaddition, with the exception of pyridine,^{29,30,34,37} isoquinoline,^{29,30} and 1,2,3-triazole *N*-arylimines.^{97,106}

N-Arylimines with reactive dipolarophiles yield the normal addition products [Eq. (16)]. The influence of electronic effects on such cycloadditions is shown by the disinclination of pyridine *N*-*p*-nitrophenylimines to react.²⁹



¹³⁹ R. Huisgen, *Angew. Chem.* **75**, 621 (1963).

¹⁴⁰ T. Okamoto, M. Hirobe, and Y. Tamai, *Chem. Pharm. Bull.* **11**, 1089 (1963).

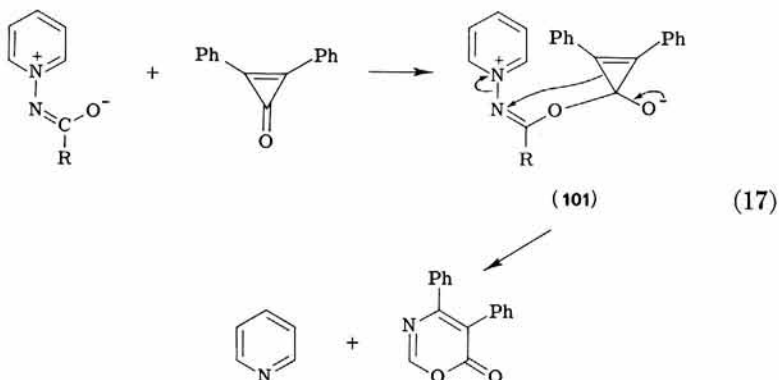
¹⁴¹ T. Okamoto, M. Hirobe, C. Mizushima, and A. Ohsawa, *Chem. Pharm. Bull.* **11**, 781 (1963).

¹⁴² V. Boekelheide and N. A. Fedoruk, *J. Org. Chem.* **33**, 2062 (1968).

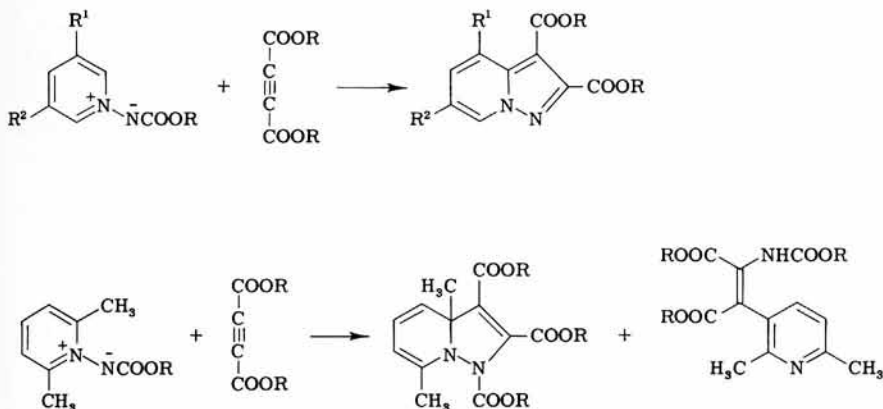
¹⁴³ T. Sasaki, K. Kanematsu, and Y. Yukimoto, *J. Chem. Soc. C*, 481 (1970).

¹⁴⁴ Y. Tamura, A. Yamakami, and M. Ikeda, *J. Pharm. Soc. Jap. (Yakugaku Zasshi)* **91**, 1154 (1971).

N-Acylimines do not yield 1,3-addition products even with the strongly dipolarophilic isocyanates [Eq. (11)]⁸⁰, but, as for 1,2-diphenylcyclopropenone,¹⁴⁵ the oxygen atom of the acylimino group is attacked. Whereas the isocyanate adduct is stable, the cyclopropenone adduct **101** reacts further as indicated in Eq. (17).



The reactions of *N*-alkoxycarbonylimines with acetylenedicarboxylic esters¹⁴⁶ are summarized in Scheme 14. *N*-Imines unsubstituted in the 2,6-positions furnish pyrazolo-pyridine only in low yield, the acyl residue of the imino group also being cleaved during the rearomatization. 2,6-Disubstituted imines in which the mesomerism between the imino group and the pyridine ring is hindered yield the normal addition products and vinylpyridine derivatives in various amounts.



Scheme 14

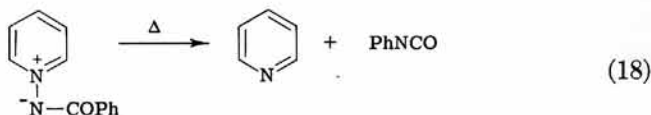
¹⁴⁵ T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.* **36**, 2451 (1971).

¹⁴⁶ T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.* **36**, 2978 (1971).

E. CLEAVAGE OF THE N-N BOND

Thermal cleavage of the N-N bond is possible, in reactions analogous to the Curtius, Hoffmann, and Lossen decompositions. Since the elimination of a tertiary amine is more difficult than that of a nitrogen molecule, the *N*-imines decompose at temperatures higher than the corresponding azides.

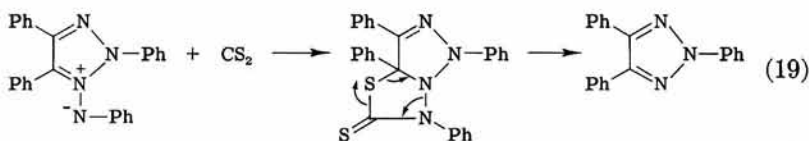
Pyridine *N*-benzoylimine decomposes at 180°–200° to pyridine and phenyl isocyanate [Eq. (18)].^{73, 128} Similarly quinoline and isoquinoline *N*-benzoylimines yield the heterocyclic base together with benzanilide, diphenylurea, and benzamide.¹²⁸ 1,2,4-Triazole *N*-acylimines also decompose on heating but do not yield isocyanates.¹⁴⁷



Easy thermal cleavage of the N-N bond in pyridine *N*-methylimines⁶⁶ has precluded isolation of such compounds. The other cleavage product, presumably methylnitrene, has not been detected or trapped, but phenylnitrene was detected in the thermal cleavage of the N-N bond of 1,2,3-triazole *N*-phenylimines.¹⁰⁶

Reductive cleavage of the N-N bond is also possible: good yields of the parent heterocycle are furnished by zinc in acetic acid,^{93, 148} SnCl₂ in hydrochloric acid,⁹³ and by catalytic hydrogenation.^{36, 78} The oxidizing power of the pyridine *N*-imine is sufficient to convert pyridines into dipyridyls.¹⁴⁹ Oxidative cleavage can also be effected, by hydrogen peroxide^{70, 71} [however, see Eq. (13)] or nitric acid.⁹⁰ Phosphorus trichloride, a typical deoxygenation reagent for *N*-oxides,^{1, 2} yields triazoles with 1,2,4-triazole 4-acylimines.¹⁴⁸ Cleavage of the N-N bond in pyridine^{34, 36, 37} and "1,2,3-triazole *N*-arylimines"¹⁰⁶ can also be effected by CS₂ [Eq. (19)]. In pyridine *N*-nitroimine, electrochemical cleavage of the N-N bond is possible.¹⁵⁰

For photochemical cleavage of the N-N bond see Section IV, G.



¹⁴⁷ H.-J. Timpe, unpublished observation.

¹⁴⁸ H.-J. Timpe, *Z. Chem.* **12**, 333 (1972).

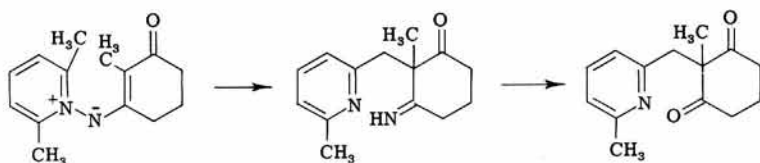
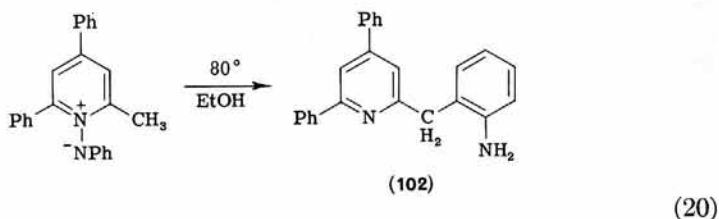
¹⁴⁹ Y. V. Kurbatov, S. V. Zalyalieva, O. S. Oschtroshenko, and A. S. Sadykov, *Arb. Samarkand. Gos. Univ.* **167**, 185 (1969); *Chem. Abstr.* **75**, 48837d (1971).

¹⁵⁰ H. Lund, *Advan. Heterocycl. Chem.* **12**, 311 (1970).

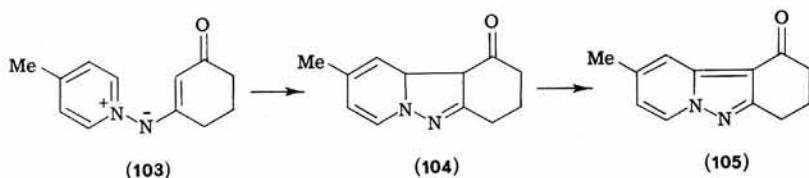
F. INTRAMOLECULAR REACTIONS

Some heteroaromatic *N*-imines possess structural elements analogous to those compounds which undergo Sommelet-Hauser rearrangements. Nevertheless, only few intramolecular rearrangement reactions of heteroaromatic *N*-imines are known.

2-(*o*-Aminobenzyl)pyridines (**102**) are generated in good yield by boiling 2-methylpyridine *N*-phenylimines in ethanol.^{34,36,37} This rearrangement is analogous to that in the reaction of α -picoline *N*-oxide with acetic anhydride.^{1,2} The precise mechanism is unknown. Pyridine *N*-imines with analogous structural elements furnish corresponding products [Eq. (20)].^{23,24,151}



Another type of intramolecular reaction of pyridine *N*-imines was described recently.^{23,24} 4-Methylpyridine *N*-(3'-oxocyclohexen-1-yl)-imine (**103**) gives 10-oxo-2-methyl-7,8,9,10-tetrahydropyrido[1,2-*b*]indazole (**105**) in boiling toluene. The reaction depends on further oxidation of the intermediate **104**. For substituted *N*-imines of type **103** ring closure involved solely the more hindered side.

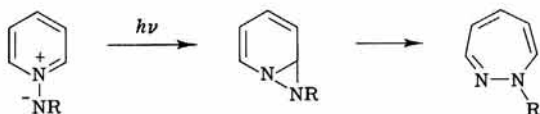


¹⁵¹ M. Michalska, *Tetrahedron Lett.*, 2267 (1971).

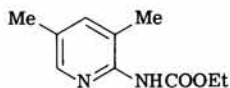
G. PHOTOCHEMICAL REACTIONS

Heteroaromatic *N*-imines are photochemically active compounds (see Table III). On irradiation they generally yield products of (a) N–N bond cleavage, (b) ring enlargement, (c) rearrangement. However, the available data do not permit definition of the conditions necessary for selective reactions. Apparently unimportant changes in the substituents and the solvent may lead to different results. Therefore, the photochemical reactions will be discussed separately for the individual *N*-imines.

Irradiation of pyridine *N*-ethoxycarbonylimine, *N*-benzoylimine, and *N*-tosylimine in methylene chloride, benzene, or methanol furnishes 1-substituted 1,2-diazepines in good yields (see Table V).^{18,19,65,67,152–156} Analogous to the photochemistry of *N*-oxides,¹⁵⁷ the formation of the seven-membered ring occurs via an intermediate diaziridine which isomerizes in a thermal reaction [Eq. (21)]. Although direct proof of this intermediate is not yet available, diaziridines are isolable on irradiation of analogous compounds with the azomethine imine structure.¹⁵⁸ This supports the pathway proposed for the heterocyclic *N*-imines.



(21)



(106)

Substituents of the imino group and the pyridine ring exert an essential influence on the decomposition of the product (see Table V). 2- and 4-Monoalkylpyridine *N*-ethoxycarbonylimines also yield only diazepines, but the corresponding *N*-acetylimines¹⁵⁶ furnish considerable amounts of N–N bond cleavage products (pyridine and methyl isocyanate). Irradiation of 3,

¹⁵² J. Streith and J.-M. Cassal, *Angew. Chem.* **80**, 117 (1968); *Angew. Chem. Int. Ed. Engl.* **7**, 129 (1968).

¹⁵³ J. Streith and J.-M. Cassal, *Tetrahedron Lett.*, 5441 (1968).

¹⁵⁴ J. Streith and C. Sigwalt, *Bull. Soc. Chim. Fr.*, 1157 (1970).

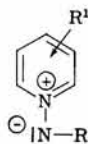
¹⁵⁵ S. Sasaki, K. Kanematsu, and A. Kakehi, *J. Chem. Soc. D*, 432 (1969).

¹⁵⁶ V. Snieckus, *J. Chem. Soc. D*, 831 (1969).

¹⁵⁷ G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.* **70**, 231 (1970).

¹⁵⁸ M. Schulz and G. West, *J. Prakt. Chem.* **312**, 161 (1970).

TABLE V

PHOTOLYSIS OF SOME PYRIDINE *N*-IMINES (WAVELENGTH ABOUT 350 nm)

R	R ¹	Solvent (reference)	Yield of products		
			Diazepine	Pyridine	Amino-pyridine
COOCH ₂ CH ₃	H	C ₆ H ₆ (65), CH ₂ Cl ₂ (19)	95.97	1	—
COOCH(CH ₃) ₂	H	CH ₂ Cl ₂ (67)	87	3	—
COOCH(CH ₃) ₂	H	CH ₂ Cl ₂ (67)	?	33	— ^a
COOCH(CH ₃) ₂	H	CH ₂ Cl ₂ (67)	?	58	— ^b
COPh	H	C ₆ H ₆ (65), CH ₂ Cl ₂ (19)	84.64	—	—
SO ₂ C ₇ H ₇	H	CH ₃ CN (65), CH ₂ Cl ₂ (19)	16.61	—	—
COCH ₃	H	CH ₂ Cl ₂ (19)	55	37	—
CSNH ₂	H	CH ₃ OH (160)	—	95	—
COOCH ₂ CH ₃	2-CH ₃	CH ₂ Cl ₂ (19)	84	—	—
COOCH ₂ CH ₃	2-CN	C ₆ H ₆ (65)	86	—	—
COCH ₃	2-CH ₃	CH ₂ Cl ₂ (157), C ₆ H ₆ (67)	60.80	33.0	—
COOCH ₂ CH ₃	4-CH ₃	CH ₂ Cl ₂ (157), C ₆ H ₆ (67)	98.75	—	—
COOCH ₂ CH ₃	4-Ph	C ₆ H ₆ (67)	92.	—	—
COOCH ₂ CH ₃	2,6-CH ₃	CH ₂ Cl ₂ (19)	72	—	—
COCH ₃	2,6-CH ₃	CH ₂ Cl ₂ (157), C ₆ H ₆ (67)	38.21	62.?	—
COOCH ₂ CH ₃	3,5-CH ₃	CH ₂ Cl ₂ (19)	41	—	31
Ph	2,4,6-Ph	CH ₂ Cl ₂ (159)	—	79	—

^a In the presence of 3,4-benzopyrene.^b In the presence of eosin.

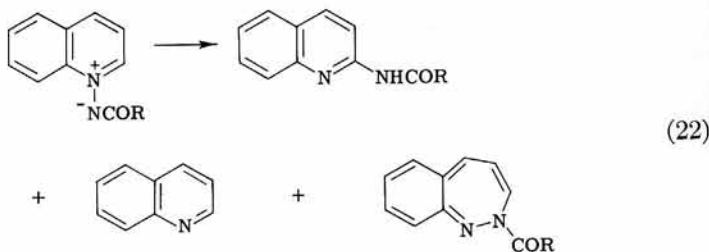
5-dimethylpyridine *N*-ethoxycarbonylimine in methylene chloride gives an aminopyridine derivative (106) in addition to the 1,2-diazepine. This compound is considered to be generated photochemically via a diaziridine intermediate.

Different excitation states are responsible for the different products of photolysis of the pyridine *N*-acylimines. Photolysis in the presence of triplet sensitizers (see Table V) led to a notable increase of N-N bond cleavage.⁶⁷ Therefore, it is assumed an excited singlet state gives rise to the isomerization process.¹²²

It is improbable that the N-N cleavage in pyridine *N*-phenylimines¹⁵⁹

and in pyridine *N*-thiocarbamoylimines¹⁶⁰ proceeds via the triplet state, since on irradiation of the *N*-arylimines singlet phenyl nitrene is formed as a second cleavage product which reacts with the solvent (methylene chloride, benzene, diethylamine) to give aniline. The singlet state of the phenyl nitrene has been proved by ESR spectroscopy and its insensitivity to oxygen.

The irradiation of quinoline *N*-acylimines yields discrepant results under analogous conditions: on the one hand all three expected products were isolated [Eq. (22)], with N-N bond cleavage prevailing;⁷⁴ according to a second report,⁷³ 2-acylaminoquinolines were isolated exclusively. Rearranged aminoisoquinolines are formed by irradiation of isoquinoline *N*-acylimines.⁷³



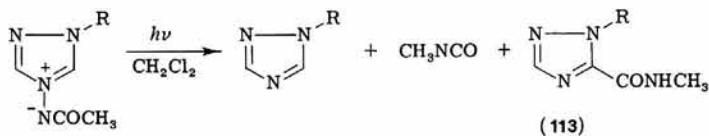
Photolysis of five-membered heterocyclic *N*-imines in most cases leads to N-N bond cleavage products, the yields being almost quantitative. Thus, irradiation of 1,2,3-triazole *N*-arylimines gives the corresponding *v*-triazole and phenyl nitrene.^{96,97,105,106} Analogous products are formed from 1,2,4-triazole 4-arylimines.¹⁶¹ The aryl nitrene formed dimerizes when oxygen is excluded to give azobenzene, and in the presence of oxygen gives azoxybenzene.

The parallel to the photochemistry of azides found in the arylimines is also observed on irradiation of 1,2,4-triazole 4-acyl,^{129,133} 4-sulfonyl,⁸¹ and 4-carbamoylimines.¹³³ In methanol the same products are generated as in the photolysis of the corresponding azides. Their formation is consistent with the mechanism given in Scheme 15: the *N*-acyl- and sulfonylimines afford 1,2,4-triazole and a nitrene which yields the typical nitrene products **107a-d** with methanol. Furthermore, carbamic esters (**109**) are formed, by addition of methanol to an isocyanate (**108**). These isocyanates can originate directly from the *N*-imine by a synchronous reaction or from the nitrene by a sextet rearrangement. Although irradiation of *s*-triazole

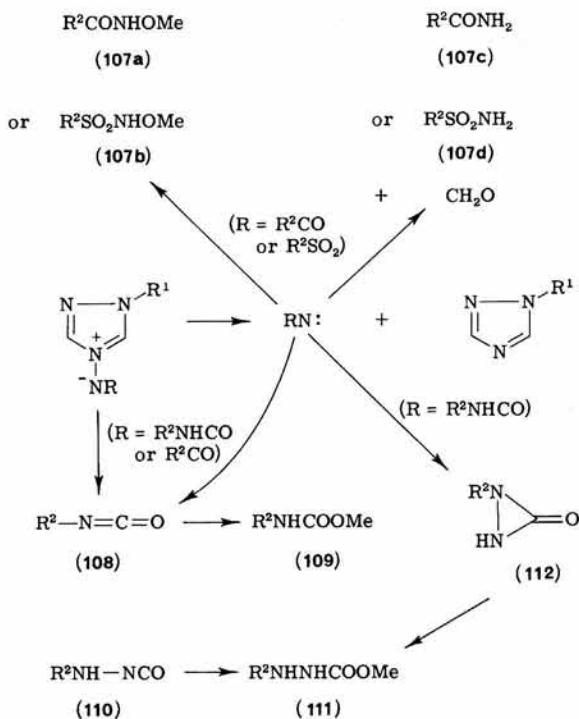
¹⁶⁰ K. T. Potts and R. Dugas, *J. Chem. Soc. D.*, 732 (1970).

¹⁶¹ C. W. Bird, D. Y. Wong, G. V. Boyd, and A. J. H. Summers, *Tetrahedron Lett.*, 3187 (1971).

4-carbamoylimines also leads to *s*-triazole, carbamidonitrenes could not be detected. The isolated hydrazine acid ester (111) can be produced by addition of methanol to an isocyanatoamine (110) as well as by methanolysis of a diaziridinone (112).



Photolysis of 1,2,4-triazole 4-acetylimines in methylene chloride gives a different product composition.¹³³ The N-N cleavage is still dominant, but *s*-triazole-5-carboxamides (113) are formed, in a rearrangement unobserved with other *N*-imines and of unknown mechanism.



Aromaticity of Heterocycles

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I. Introduction

At a time when the validity of the concept of aromaticity is questioned, increasingly, it seems appropriate to review various definitions in common use and to survey their applications in heterocyclic chemistry.

From a qualitative viewpoint the characteristics of an aromatic compound are easy to define. A compound is said to be aromatic if it is cyclic and unsaturated with an enhanced stability over simple olefinic compounds. In particular it tends to react by substitution rather than addition, or in other words it "maintains the type" as succinctly expressed in the phrase

of Sir Robert Robinson,¹ and thus regains after the reaction the aromatic sextet of π -electrons. To be more precise, aromatic compounds are associated with the presence of $4n + 2$ π -electrons (the Hückel rule),² and the degree of aromatic character that can be attributable to a particular heterocyclic compound (of the nonpyridinoid type) is associated, at least in part, with the facility by which the electrons of the heteroatom become involved in a delocalized π -electron system.

The characteristic aromatic reactivity of the type described above is clearly a matter of degree and is difficult to assess quantitatively. From a simple consideration of pyridine, which reacts less readily with electrophiles but more readily with nucleophiles at the ring carbon atoms than does benzene, it soon becomes apparent that attempts to discuss even relative aromatic character using kinetic criteria is fraught with difficulties; this is apart from the fundamental objection that chemical reactivity is not solely a function of ground-state stability. More success at quantifying aromatic character has been forthcoming from a closer examination of the delocalized π -electron system and the characteristic physicochemical properties which are derived from it, such as the enhanced stability, the particular molecular geometry, magnetic anisotropy, and diamagnetic susceptibility exaltation. In the first part of this review we survey some of the semiempirical and theoretical approaches of this type that have been applied or are potentially applicable to heteroaromatic compounds, and in the remainder we survey some conclusions drawn from their application to various classes of compounds generally regarded as being aromatic. A full discussion of antiaromatic ($4n$ π -electron systems) and homoaromatic heterocyclic compounds we believe to be outside the scope of the present review and only occasional passing reference is made to these in the text.

The material for this review has been drawn essentially from literature up to the end of 1971. However, some relevant and interesting studies reported in 1972, which came to our attention during the preparation of this article, have also been included.

II. Methods Available for Assessing Aromaticity

A. ENERGETIC CRITERIA

There is a profusion of terms used in the literature to refer to the enhanced stability of a compound over that of a hypothetical molecule of

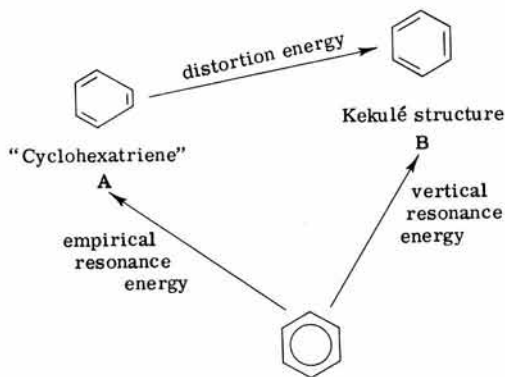
¹ J. W. Armit and R. Robinson, *J. Chem. Soc.* **127**, 1604 (1925).

² E. Hückel, *Z. Phys.* **70**, 204 (1931); **72**, 310 (1931).

the same gross structure but lacking π -electron delocalization. "Stabilization energy," "resonance energy," "empirical and vertical resonance energy," "delocalization energy," "conjugation energy," "binding energy" are terms which appear regularly. Some authors have defined important differences between some of these while others use the very same terms as synonyms. In an attempt to avoid confusion and without necessarily implying a greater desirability of the use of one term over another we use *delocalization energy* (DE) for the energy term calculated by MO theory, and *empirical resonance energy* (ERE) as far as possible for the energy derived by experimental methods and as defined below. Modifications of the treatment of the experimental data have at times required the use of other terminology and this is defined in the text where appropriate.

1. Empirical Resonance Energy

Scheme 1 illustrates the distinction between two terms in common usage: the empirical resonance energy (ERE) and the vertical resonance energy. The former is the energy difference between the real structure and a localized structure of type A (for benzene) and is classically derived from comparison of thermochemical data for the real structure with data from models for the localized structure. Models used are normally simple unsaturated compounds. Vertical resonance energy is the energy difference between the actual structure and a localized structure (B) in which the atom positions are the same as in the real molecule. The vertical resonance energy is perhaps the more significant to theoreticians because it is these structures that are used in MO calculations of delocalization energy (Section II,A, 3). The difference between the empirical and vertical resonance energies is the distortion energy required to compress the single bonds and stretch the double bonds in going from structure A to B.



Scheme 1

Attempts have been made to estimate the distortion energy for benzene: Coulson^{3a} obtained a value of 27 kcal mole⁻¹ and Mulliken and Parr^{3b} a value of 37 kcal mole⁻¹. In ERE determinations the unsaturated models themselves are often less than ideal and Dewar and Schmeising⁴ have pointed out that a carbon-carbon single bond between an sp^3 and an sp^2 carbon is of different energy from one between two sp^3 carbon atoms and therefore a hybridization energy term may be contained in the thermochemical quantities. These and further problems associated with the estimation of vertical resonance energy have been recognized for some time and are well reviewed by Streitwieser.^{5a}

a. *Experimental Approaches.* ERE values for heteroaromatic systems have, in the main, been obtained from heat of combustion and heat of hydrogenation data. The difficulty in quantitatively hydrogenating many heterocycles has rendered the latter approach rather less generally applicable than the former. Errors in the experimental determination of heats of combustion are normally of the order of 0.5 kcal mole⁻¹—and are somewhat larger than those of heat of hydrogenation data. More serious uncertainty in earlier determinations may have arisen during the estimation of the thermochemical data for the localized model, particularly when calculating heat of formation from values of bond energies for bonds between carbon and heteroatoms where the reliability was, and at times still is, questionable. Calculations normally rely further on the assumption that thermochemical bond energy terms are additive. Many of the literature data for various systems are collected in Tables I and II.⁶

Cox⁷ has refined the calculation of heats of atomization of the localized structures by taking into account that (1) the C-X bond energy depends

^{3a} C. A. Coulson and S. L. Altmann, *Trans. Faraday Soc.* **48**, 293 (1952).

^{3b} R. J. Mulliken and R. G. Parr, *J. Chem. Phys.* **19**, 1271 (1951).

⁴ M. J. S. Dewar and H. N. Schmeising, *Tetrahedron* **5**, 166 (1959); **11**, 96 (1960).

⁵ (a) A. Streitwieser, Jr. in "Molecular Orbital Theory for Organic Chemists," p. 237 Wiley, New York, 1967; (b) *ibid.*, p. 246.

⁶ (a) R. Klages, *Chem. Ber.* **82**, 358 (1949); (b) H. Grasshof, *ibid.* **84**, 916 (1951); (c) L. Pauling and J. Sherman, *J. Chem. Phys.* **1**, 606 (1933); (d) G. W. Wheland, in "Resonance in Organic Chemistry," p. 75. Wiley, New York, 1955; (e) J. L. Franklin, *J. Amer. Chem. Soc.* **72**, 4278 (1950); (f) A. F. Bedford, A. E. Beezer, and C. T. Mortimer, *J. Chem. Soc.*, 2039 (1963); (g) J. Tjebbes, *Acta Chem. Scand.* **16**, 916 (1962); (h) S. Sunner, *ibid.* **9**, 847 (1955); (i) H. Zimmermann and H. Geisenfelder, *Z. Elektrochem.* **65**, 368 (1961); (j) A. F. Bedford, D. M. Heinekey, J. T. Millar, and C. T. Mortimer, *J. Chem. Soc.*, 2932 (1962); (k) L. Pauling, in "The Nature of the Chemical Bond," p. 3. Cornell Univ. Press, Ithaca, New York, 1960; (l) T. L. Cottrell, in "The Strength of Chemical Bonds," p. 236. Butterworths, London, 1954; (m) G. E. Coates and L. E. Sutton, *J. Chem. Soc.*, 1187 (1948).

⁷ J. D. Cox, *Tetrahedron* **19**, 1175 (1963).

TABLE I
EMPIRICAL RESONANCE ENERGY DATA (KCAL MOLE⁻¹) FOR
AZINES AND FIVE-MEMBERED RING COMPOUNDS CONTAINING ONE HETEROATOM

	Ref. 6a		Ref. 6b		Ref. 6d				Ref. 7	
	Method		Method		Method		Method		Ref. 6f	Ref. 6g
	A ^a	B ^a	A ^a	B ^a	A ^a	C ^a	B ^a	D ^a		
Benzene	35.9	36.8	36	36.8	36	36.4	36.0	36	—	40.8
Naphthalene	61.0	—	61.6	—	61.0	61.2	—	62	—	—
Pyridine	27.9	—	—	—	23	—	—	—	32.0	24.2
Pyridazine	—	—	—	—	—	—	—	—	—	12.3
Pyrimidine	—	—	—	—	—	—	—	—	—	8.0
Pyrazine	—	—	—	—	—	—	—	—	24.0	8.1
Quinoline	48.4	—	—	—	47.3	—	—	—	—	—
Thiophene	29.1	—	24.1	—	28.7	27.7	—	31	—	16 ^b
Furan	16.2	—	17	21.1	15.8	22.2	17.2	23	—	8
Pyrrole ^c	21.6	—	14	—	21.2	24.5	—	27	—	15
Indole ^c	—	—	—	—	47	49	—	—	—	—
Carbazole ^c	—	—	—	—	74	75	—	—	—	—

^a A, Via heats of combustion; B, via heats of hydrogenation; C, values obtained using different bonding data; D, conjugation energy (see text).

^b Cf. 20 kcal mole⁻¹ (Sunder ^{9b}).

^c For further data see Table II.

TABLE II

EMPIRICAL RESONANCE ENERGY DATA (KCAL MOLE⁻¹) FOR AZOLES

	Ref. 6i					Ref. 7	
	Method A ^a	Method B ^a	Method C ^a	Method D ^a	Method E ^a	Ref. 6j	Method F ^a
Pyrrole ^b	28.5	22.1	17.4	27.6	30.9	—	15
Pyrazole	41.5	26.8	32.7	—	—	29.3	27
Imidazole	32.1	12.7	17.7	22.3	—	14.2	27
1,2,4-Triazole	49.2	20.0	36.2	—	—	—	—
Tetrazole	—	55.2	63.1	—	—	—	—
Indole ^b	57.6	52.0	41.8	51.0	53.8	—	—
Indazole	73.9	59.0	59.5	—	—	—	—
Benzimidazole	68.8	48.7	48.8	52.3	—	—	—
Benzotriazole	—	82.9	74.7	—	—	—	—
Carbazole ^b	100.7	94.9	79.2	87.4	89.7	—	—

^a A, Results obtained using Pauling's bond energy terms^{6k}; B, using the bond energy terms reported by Cottrell^{6l}; C, using Coates and Sutton's bond energy terms^{6m}; D, results calculated using Klage's approach^{6a}; E, results calculated using Franklin's approach^{6e}; F, conjugation energy, see text.

^b For further data see Table I.

upon the hybridization of the carbon atom, (2) there are energy differences between primary, secondary, and tertiary C-H bonds, and (3) there are strong "next-nearest-neighbor" interactions in oxygen ring compounds. Comparison of these refined values with literature values for the heats of formation of the actual compounds affords an energy term which the author, after Dewar, calls the "conjugation energy" (Table I). Further extensive calculations using heat of atomization data have been published by Dewar *et al.*⁸⁻¹³ and are discussed in Section II,A, 2. The application of tautomeric equilibrium data for evaluating ERE differences between two tautomers is considered in Section II,A, 4.

In spite of the problems outlined above the determinations of empirical resonance energies have provided one of the widest ranging and most often

⁸ M. J. S. Dewar, *Tetrahedron* **22**, Suppl. 8, 75 (1966).

⁹ M. J. S. Dewar, A. J. Harget, and N. Trinajstić, *J. Amer. Chem. Soc.* **91**, 6321 (1969).

¹⁰ M. J. S. Dewar and N. Trinajstić, *J. Amer. Chem. Soc.* **92**, 1453 (1970).

¹¹ M. J. S. Dewar and N. Trinajstić, *Tetrahedron* **26**, 4269 (1970).

¹² M. J. S. Dewar, A. J. Harget, N. Trinajstić, and S. D. Worley, *Tetrahedron* **26**, 4505 (1970).

¹³ M. J. S. Dewar and N. Trinajstić, *Theor. Chim. Acta* **17**, 235 (1970).

quoted series of data for assessing the aromatic character of heteroaromatic systems on a quantitative basis.

2. "Dewar Resonance Energy"

Dewar and co-workers^{8,9} have proposed a modified definition of resonance energy which avoids some of the problems associated with defining a resonance energy in terms of energies of pure single and double bonds outlined above. The *Dewar resonance energy* is defined as the difference in the heat of atomization between a given conjugated cyclic molecule and the energy of the appropriate open-chain polyene. It is argued that this definition is superior to others for the following reasons:

(a) The quantities which chemists are primarily interested in concerning aromatic molecules are not necessarily their stability relative to some idealized structure with pure single and double bonds, but rather their stability relative to an open-chain analog.

(b) The definition is independent of theoretical approaches because the polyene bond energies can be estimated from thermochemical data.

In the absence of experimental data of the type required the authors have in fact been obliged to resort to some theoretical calculations using a semiempirical SCF-MO method. The resonance energies of many heterocyclic systems have been determined and results are listed in Table III. In all papers by Dewar *et al.* the results are discussed in terms of the experimentally observed reactivity and stability of the systems. An independent calculation¹⁴ has given a somewhat different value for furan (12.5 kcal mole⁻¹) but a very similar one for dibenzofuran (43.7 kcal mole⁻¹). During the latter stages of the preparation of this article, Hess, Schaad, and Holyoke¹⁵ reported the application of the HMO method to the calculation of heats of atomization and resonance energy of a range of five-, seven-, and nine-membered ring oxygen and nitrogen heterocycles.

In an extension Dewar and co-workers¹⁶ have calculated the heats of atomization for many potentially tautomeric compounds and the differences in the values for tautomeric forms are compared with the available experimental equilibrium constants. This and other work on the relationship between tautomeric equilibria and stability of the tautomeric forms of heteroaromatics is discussed further below (Section II,A, 4).

Dewar resonance energy determinations would appear to be derived from a much more rigorous manipulation of thermochemical data than many of the earlier resonance energy determinations.

¹⁴ N. C. Baird, *Can. J. Chem.* **42**, 3535 (1969).

¹⁵ B. A. Hess, L. J. Schaad, and C. W. Holyoke, *Tetrahedron* **28**, 3657 (1972).

¹⁶ N. Bodor, M. J. S. Dewar, and A. J. Harget, *J. Amer. Chem. Soc.* **92**, 2929 (1970).

3. Delocalization Energy

In MO theory the delocalization energy (DE) is the calculated additional bonding energy associated with the delocalization of π -electrons originally constrained in isolated double bonds, and thus corresponds to vertical resonance energy. It is not the purpose of this review to discuss the approximations and refinements that have been made to the MO method, but the cautionary comments of Dewar¹⁷ are perhaps worth noting here. In Dewar's view the HMO method is so unreliable as to be useless in treating heterocyclic compounds and hydrocarbons that are either nonaromatic or contain an odd-membered ring. However, in spite of its undoubted limitations extensive application of the simple Hückel MO theory to heterocyclic compounds has and still is made and indeed often provides a basis for the understanding of the electronic effects within systems (for a recent defense of the HMO method for the calculation of heats of atomization and resonance energies see Hess *et al.*¹⁵).

DE is expressed in terms of β , the exact value of which is uncertain (for a recent discussion see Figeys¹⁸ and Sannigrahi¹⁹). Plots of DE (in units of β) against ERE for hydrocarbons give good straight lines and it has been pointed out^{5b} that such correlations must require a remarkable proportionality between distortion energies (Section II,A, 1) and ERE values. For heterocyclic compounds, however, the nonlinearity of DE versus ERE plots has been reported.²⁰ It appears that of various six-membered nitrogen heterocycles, pyridine and quinoline obey an equation $ERE = 15.8 DE$, whereas pyridazine, pyrimidine, and pyrazine do not.

In a relatively early paper, Orgel *et al.*,²¹ in estimating the DE of pyridine, pyrimidine, pyrazine, and pyrrole, pointed out the difficulty in calculating the energy of the classical structure when the structure to be chosen as a reference becomes less obvious. DE data have, however, been reported for a wide range of heterocyclic compounds including phosphole, pyrrole,²² indole,²³ indazole,²³ tautomeric azoles,²² tetraazapentalenes,²⁴ cyclazine,^{25,26}

¹⁷ M. J. S. Dewar, *Chem. Soc. Spec. Publ.* **21**, 177 (1967).

¹⁸ H. P. Figeys, *Tetrahedron* **26**, 4615, 5225 (1970).

¹⁹ A. B. Sannigrahi and A. K. Kar, *Tetrahedron* **25**, 3243 (1969).

²⁰ R. Zahradník and J. Koutecký, *Advan. Heterocycl. Chem.* **5**, 69 (1965).

²¹ L. E. Orgel, T. L. Cottrell, W. Dick, and L. E. Sutton, *Trans. Faraday Soc.* **47**, 113 (1951).

²² A. J. Owen, *Tetrahedron* **14**, 237 (1961).

²³ O. E. Polansky and M. A. Grassberger, *Monatsh. Chem.* **94**, 662 (1963).

²⁴ R. A. Carboni, J. C. Kauer, J. E. Castle, and H. E. Simmons, *J. Amer. Chem. Soc.* **89**, 2618 (1967).

²⁵ R. J. Windgassen, W. H. Saunders, and V. Boekelheide, *J. Amer. Chem. Soc.* **81**, 1459 (1959).

²⁶ R. D. Brown and B. A. W. Collier, *Mol. Phys.* **2**, 158 (1959).

TABLE III
DEWAR RESONANCE ENERGY DATA (KCAL MOLE⁻¹)^{a, b}

Azines ^c					
Benzene	22.6 (20.04) ⁹	Naphthalene	33.6 (30.51) ⁹	1,8-Naphthyridine	36.4 (27.07) ⁹
Pyridine	23.1 (20.94) ⁹	Quinoline	34.1 (32.95) ⁹	Quinoxaline	28.1 (25.41) ⁹
Pyrazine	17.1 (14.64) ⁹	Isoquinoline	34.1	Quinazoline	30.39 ⁹
Pyrimidine	20.20 ⁹	1,5-Naphthyridine	33.2 (31.09) ⁹	Acridine	41.3
Three- and Five-Membered Rings ^d					
Oxirene	-5.5 ¹³	2-Azirene	-6.7 ¹³	Thiophene	6.5
Furan	4.3 ¹³ (1.59) ⁹	Pyrrrole	5.3 ¹³ (8.53) ⁹	Benzo[b]thiophene	24.8
Benzo[b]furan	20.3 ^{12,9}	Indole	23.8 ¹²	Benzo[c]thiophene	9.3
Benzo[c]furan	2.4 ¹²	Isoindole	11.6 ¹²	Dibenzothiophene	44.6
Dibenzofuran	39.9 ^{12,9}	Carbazole	40.9 ¹²	1,4-Thiophthene	11.3
		Imidazole	15.43 ⁹	1,5-Thiophthene	5.9
		Benzimidazole	30.90 ⁹		

Seven-membered rings^a

Pyrrolidine 6.9¹³
 1,6-Thiophthene 10.5
 2,5-Thiophthene -33.9
 2,2'-Bithienyl 12.7
 2,3'-Bithienyl 12.1
 3,3'-Bithienyl 11.0

Oxepin	0.12	Azepine	-1.80	Thiepin	-1.45 ¹⁰
4,5-Benzoxepin	18.77	4,5-Benzazepine	17.53	4,5-Benzothiepin	19.9 ¹⁰
3,4-Benzoxepin	1.15	3,4-Benzazepine	-0.78	Thieno[<i>c</i> , <i>d</i>]thiepin	3.5 ¹⁰
2,3-Benzoxepin	19.95	2,3-Benzazepine	18.36		
2,3,5,6-Dibenzoxepin	20.94	2,3,5,6-Dibenzazepine	19.49		
2,3,6,7-Dibenzoxepin	39.80	2,3,6,7-Dibenzazepine	38.40		
2,3,4,5-Dibenzoxepin	39.03	2,3,4,5-Dibenzazepine	37.89		
3,4,5,6-Dibenzoxepin	3.14	3,4,5,6-Dibenzazepine	1.08		
Tribenzoxepin	59.27	Tribenzazepine	58.14		

^a Values in parentheses are data which have subsequently been modified in the light of the discussion by Dewar and Trinajstić.¹³

^b For values of amino-substituted pyridines and phenyl-substituted benzo-fused heteroaromatic see Dewar *et al.*^{13,12}

^c Data from Dewar and Trinajstić¹³ except where otherwise indicated.

^d Data from Dewar and Trinajstić¹⁰ except where otherwise indicated.

^e Data from Dewar and Trinajstić¹¹ except where otherwise indicated.

azines,^{22,27} 2- and 4-pyrone,^{28,29} 2-thiapyrone, 2-thiopyrone, and 2-thiothiapyrone,²⁹ thiopyrylium ion,³⁰ benzo-1,3-dithiolium ion,³¹ naphthyridine,³² and the heterocyclic analogs of fluoranthene.³³

a. *Specific Delocalization Energy*, DE_{sp} . Specific delocalization energy is derived by averaging the DE over the number of π -electrons or atoms in conjugation, or the number of C-C bonds over which the conjugated system extends. DE_{sp} , unlike DE, does not increase markedly within the series benzene, naphthalene, anthracene and has been regarded as being better suited for discussing aromaticities of hydrocarbons than DE itself.³⁴ DE_{sp} for pyridine has been calculated³⁵ to be 0.350 and is marginally larger than that for benzene. Data for pyrones are reported in Section III,D, 6 but general application to heteroaromatic compounds does not appear to have been developed.

4. Tautomeric Equilibria and Resonance Stabilization

Many ring-substituted heterocycles exist in more than one tautomeric form, and heteroaromatic tautomeric equilibria have been the subject of a number of theoretical discussions. Mason³⁶ has found a good correlation between the equilibrium constants (K_T) and π -electron energies of various pyridones, quinolones, isoquinolones, etc., and further calculations by a Russian group³⁷ on compounds of this type are also in agreement with experimental findings. K_T for various amino pyridines have been estimated²³ from the results of LCAO-MO calculations and are found to be in general agreement with experimental data. Kuthan *et al.*,³⁸ using the HMO method, reported that the trend in the tautomeric equilibria in the series **1** and **2** (where X = O, S, NH, CH₂; R = H) show poor correlation with π -electron energy differences between the tautomers, but good correlation with delocalization energy differences. Results of HMO

²⁷ J. H. Reynolds, *Diss. Abstr.* **25**, 6968 (1965).

²⁸ P. Beak, *Tetrahedron* **20**, 831 (1964).

²⁹ R. Zahradník, C. Párkányi, and J. Kouřecký, *Collect. Czech. Chem. Commun.* **27**, 1242 (1962).

³⁰ J. Kouřecký, *Collect. Czech. Chem. Commun.* **24**, 1608 (1959).

³¹ J. Kouřecký, J. Paldus, and R. Zahradník, *Collect. Czech. Chem. Commun.* **25**, 617 (1960).

³² W. W. Paudler and T. J. Kress, *J. Org. Chem.* **33**, 1384 (1968).

³³ M. Scholz and D. Heidrich, *Z. Chem.* **7**, 349 (1967).

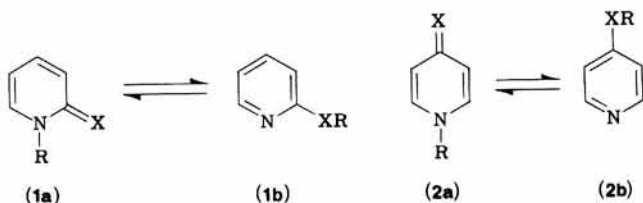
³⁴ R. Zahradník, J. Michl, and J. Pancir, *Tetrahedron* **22**, 1355 (1966).

³⁵ J. Kruszewski and T. M. Krygowski, *Tetrahedron Lett.*, 319 (1970).

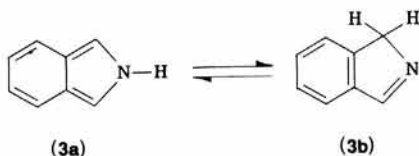
³⁶ S. F. Mason, *J. Chem. Soc.*, 674 (1958).

³⁷ V. P. Zvolinskii, M. E. Perel'son, and Yu. N. Sheinker, *Dokl. Phys. Chem.* **179**, 257 (1968); *Teor. Ekspr. Khim. (USSR)* **6**, 250 (1970).

³⁸ J. Kuthan, V. Skala, and J. Paleček, *Z. Chem.* **8**, 305 (1968).



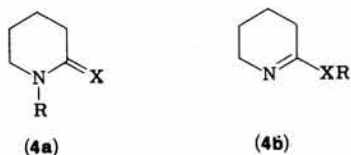
calculations have been advanced to predict that isoindole–isoindolenine equilibria (**3a** \rightleftharpoons **3b**) should favor the isoindole form.^{39,40}



In a wide-ranging study Dewar and co-workers¹⁶ have recently used their semiempirical SCF–MO method (Section II,A,2) to calculate the heats of atomization of the tautomers of many hydroxy and imino derivatives of five- and six-membered ring heteroaromatics. The calculated relative stabilities of the forms are in good general agreement with experimental findings; odd discrepancies can be attributed at least in part to the fact that the calculations refer to the gaseous phase, whereas the majority of experimental measurements have been obtained in aqueous media.

Two groups have applied a reverse procedure and estimated quantitatively the difference in empirical resonance energy between two tautomeric forms by comparing the equilibrium of the heteroaromatic with that of a model for the hypothetical localized system. Scheme 2 illustrates the relationship for the pyridone system.

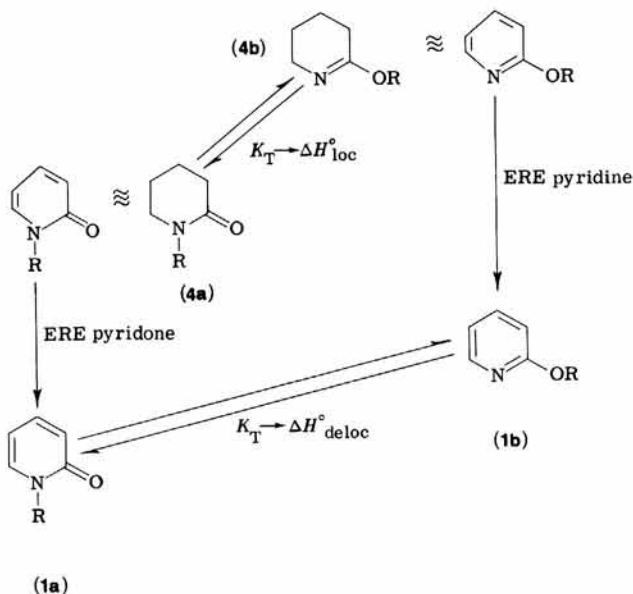
In the more rigorous of the two approaches Beak *et al.*⁴¹ determined calorimetrically ΔH° for the equilibrium between *N*-methyl-2-pyridone (**1a**, R = Me) and 2-methoxypyridine (**1b**, R = Me) ($\Delta H_{\text{deloc}}^\circ$) and also for that between the saturated analogs (**4a**, **4b**, R = Me) ($\Delta H_{\text{loc}}^\circ$). Equilibrations were performed using catalytic amounts of the appropriate



³⁹ D. F. Veber and W. Lwowski, *J. Amer. Chem. Soc.* **86**, 4152 (1964).

⁴⁰ J. Kopecky, J. E. Shields, and J. Bornstein, *Tetrahedron Lett.*, **3669** (1967).

⁴¹ P. Beak, J. Bonham, and J. T. Lee, *J. Amer. Chem. Soc.* **90**, 1569 (1968).



Scheme 2

common alkylated derivatives. The ERE of 2-methoxypyridine was found to be 6 ± 7 kcal mole⁻¹ greater than that of *N*-methylpyridone. The method, however, appears to be of limited applicability because of difficulties in equilibrating the aliphatic models required for other determinations.⁴² By contrast Katritzky and co-workers⁴³ compare the corresponding protomeric equilibria ($1a \rightleftharpoons 1b$, $R = H$ and $4a \rightleftharpoons 4b$, $R = H$) for which many quantitative data are already available. The method has been extended to 4-pyridthione, 4-pyridoneimine, and 4-pyridmethide, and to the corresponding quinolonoid and isoquinolonoid series.⁴⁴ Empirical resonance energy differences deduced in this way are listed in Table IV.

5. Acidity, Basicity, Pseudo-Base Equilibria, and Resonance Energy

Wheland⁴⁵ demonstrated the relationship between MO delocalization energy of hydrocarbons and their acidity, and on this basis Streitwieser⁴⁶

⁴² P. Beak and J. T. Lee, *J. Org. Chem.* **34**, 2125 (1969).

⁴³ M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *J. Chem. Soc., Perkin Trans. II*, 1295 (1972); *Chem. Commun.*, 510 (1971).

⁴⁴ M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *J. Chem. Soc., Perkin Trans. II*, 1080 (1973).

⁴⁵ G. W. Wheland, *J. Chem. Phys.* **2**, 474 (1934).

⁴⁶ A. Streitwieser, Jr., *Tetrahedron Lett.* **6**, 23 (1960).

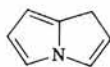
TABLE IV

RESONANCE ENERGY DIFFERENCES FOR THE 2- AND 4-PYRIDONE, 2-QUINOLONE, AND 1-ISQUINOLONE SERIES FROM TAUTOMERIC EQUILIBRIUM DATA^{43,44}

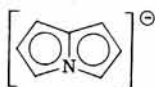
X	$(A_{py} - A_x)^a$ (kcal mole ⁻¹)		$(A_q - A_x)$ (kcal mole ⁻¹)	$(A_{isoq} - A_x)$ (kcal mole ⁻¹)
	2-Series	4-Series		
O	7.5±1	7.7±1.5	2.0±0.5	4.4±1.0
S	6 ±1	—	2.9±0.5	4.0±1.0
NH	10 ±2	14.5±3	5.0±1.0	6.2±1.2
CH ₂	17.5±3.5	19.5±4	7.9±1.5	7.4±1.5

^a $A_{py} - A_x$ is the difference in resonance energy between the pyridine and pyridonoid structures, x referring to the exocyclic atom or group in the latter. Similar nomenclature follows for the benzo-fused series.

correlated ΔM , the differences in DE between the anion and hydrocarbon, with pK_a . Applications to the heterocyclic systems appear to be few. Okamura and Katz⁴⁷ estimated the pK_a of 3*H*-pyrrolizine (5) to be 2.9, which corresponds to a ΔM between 5 and the anion 6 of 1.1 units. ΔM



(5)



(6)

calculated by simple MO theory was $\Delta 1.3$. For further qualitative applications of this approach see Sections III, E, 2 and III, F, 2.

The low basicity of 1-methylphosphole⁴⁸ and pyrrole⁴⁹ may be accounted for by the loss of resonance energy in going to the protonated form. Indeed comparison of the pK_a of *N*-methylpyrrole in both the α - and β -positions with those estimated for nonaromatic models, e.g. (7) and (8) which give cations (9) and (10) of similar electronic structure to the cations (11) and (12) from pyrrole, allow the ERE of this heteroaromatic to be estimated as ~ 27 kcal mole⁻¹.^{50, 51} A similar approach has been discussed for

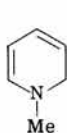
⁴⁷ W. H. Okamura and T. J. Katz, *Tetrahedron* **23**, 2941 (1967).

⁴⁸ L. D. Quin, J. G. Bryson, and C. G. Moreland, *J. Amer. Chem. Soc.* **91**, 3308 (1969).

⁴⁹ F. Klages, *Chem. Ber.* **82**, 358 (1949).

⁵⁰ M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *Tetrahedron Lett.*, 5019 (1972).

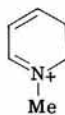
⁵¹ D. Lloyd and D. R. Marshall, *Chem. Ind. (London)*, 335 (1972).



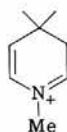
(7)



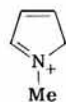
(8)



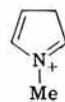
(9)



(10)

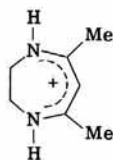


(11)



(12)

indole,^{50, 51} carbazole,⁵⁰ and the 2,3-dihydro-1*H*-1,4-diazepinium cation (13).⁵¹



(13)

In yet a further application of equilibrium data, the ΔH° for pseudo-base formation of isoquinolinium methiodide has been compared with corresponding data for 3,4-dihydroisoquinolinium methiodide, leading to a value of 48 ± 9 kcal mole⁻¹ for the ERE of the former.⁵⁰

B. STRUCTURAL CRITERIA

The assessment of aromatic character from structural criteria would appear to be a very valid approach. Aromatic π -electron delocalization requires planarity of the aromatic molecule and leads to a typical carbon-carbon bond length intermediate between that of a single bond and a formal olefinic double bond. Indeed qualitative orders of the aromaticity of five-membered heteroaromatics have been derived from a consideration of the relative degree of "diene character" of the conjugated system as assessed from structural determinations of bond lengths (see, for example, Sections III,C, 1 and 5).

TABLE V
AROMATICITY INDICES A_1^{52} AND A^{55}

Compound	A_1	A
Benzene	1	1
Thiophene	0.93	0.67
Pyrrole	0.91	0.38
Furan	0.87	0.06
Pyridine	1.00 ^a	0.97
2-Pyrone	0.79, 0.96 ^b	—
4-Pyrone	0.72, 0.94 ^b	—

^a Data from Pujol and Julg⁵³ and Kruszewski and Krygowski.⁵⁵

^b Hérault and Gayoso.⁵⁴ Values obtained from two sets of MO-calculated bond lengths.

Julg and co-workers have attempted to use structural criteria as a quantitative tool for assessing aromatic character and they have developed⁵² an aromaticity index A_1 which is a measure of the degree of averaging of the peripheral bonds in an aromatic skeleton. The index is defined as

$$A_1 = \frac{1-225}{\mu} \sum_r \left[\frac{1-d_r}{\bar{d}} \right]^2$$

where \bar{d} is the mean bond length, d_r is the length of bond r , and μ is the number of π -electrons in the ring. From the constants used, the A_1 value of benzene is 1, and values for heteroaromatics^{55, 52-54} are given in the Table V.

Recently the approach has been refined⁵⁵ to allow for the resistance to circulation of the π -electrons, which is said to be particularly apparent when electronegative atoms are present in the ring. The resistance is expressed in terms of a charge gradient, $\Delta q_{ij}/d_{ij}$, where Δq_{ij} is the difference in π -charges at the atoms i and j , and d_{ij} is the distance between them. An aromaticity correction factor, A_2 , is then given by

$$A_2 = \prod_{(ij)} [1 - B(\Delta q_{ij}/d_{ij})^2]$$

⁵² A. Julg and P. François, *Theor. Chim. Acta* **8**, 249 (1967).

⁵³ L. Pujol and A. Julg, *Tetrahedron* **21**, 717 (1965).

⁵⁴ V. Hérault and J. Gayoso, *C. R. Acad. Sci.* **269**, 298 (1969).

⁵⁵ A. Julg, in "Aromaticity, Pseudo-aromaticity, Anti-aromaticity," Jerusalem Symp. Quant. Chem. Biochem., 1970, (E. D. Bergmann and B. Pullman, eds.), Vol. III, p. 383. Israel Acad. Sci. Humanities, Jerusalem, 1971.

In this expression B is a constant and set at 1. Values for the corrected aromaticity constant $A = A_1 A_2$ for heteroaromatics are given in Table V.

A theoretical approach similar to Julg's approach, but which has not apparently been applied to heterocyclic compounds has been developed by Kemula and Krygowski⁵⁶ and is based on bond order rather than bond lengths.

In the same vein, Krongauz *et al.*⁵⁷ have assessed calculated bond alternation in various five-membered ring heteroaromatics and concluded that the sulfur-containing ring systems are normally more aromatic than the oxygen and nitrogen counterparts. Thus 1,3,4-thiadiazole shows little bond alternation, whereas oxadiazoles show more and are evidently much less aromatic, 1,2,4-oxadiazole being still less energetically favorable than 1,3,4-oxadiazole. From the bond equivalence criterion an order of decreasing aromatic character—thiophene, selenophene, furan—can be deduced,⁵⁸ and Bak *et al.*⁵⁹ using bond order arguments based on microwave data report a decreasing scale of aromaticity in the sequence 1,2,5-thiadiazole, thiophene, 1,3,4-thiadiazole, 1,2,5-oxadiazole. The near "normal" O–N bond length in the oxadiazole has been taken as an indication that this molecule has a low degree of aromaticity. The structural criterion has been developed further by Binsch and co-workers,^{60,61} who propose that a conjugated system is aromatic if it shows neither strong first-order nor second-order, double-bond fixation. From SCF calculations they conclude that aza and diaza analogs of pentalene and heptalene should be nonaromatic.

C. THE ELECTRONIC MODEL

The concept of aromaticity is closely linked to the concept of electron delocalization, and several methods of investigation of electronic structure have been used as criteria of aromaticity, although these methods have been used principally in qualitative terms.

1. Photoelectron Spectroscopy

The application of ESCA to the investigation of aromaticity is based on the known sensitivity of the binding energies of core electrons to

⁵⁶ W. Kemula and T. M. Krygowski, *Tetrahedron Lett.*, **5135** (1968).

⁵⁷ E. S. Krongauz, D. A. Bochvar, J. V. Stankevich, and V. V. Korshak, *Dokl. Chem.* **179**, 190 (1968).

⁵⁸ N. N. Magdesieva, *Advan. Heterocycl. Chem.* **12**, 1 (1970).

⁵⁹ B. Bak, L. Nygaard, E. J. Pedersen, and J. Rastrup-Andersen, *J. Mol. Spectrosc.* **19**, 283 (1966).

⁶⁰ G. Binsch and E. Heilbronner, *Tetrahedron* **24**, 1215 (1968).

⁶¹ G. Binsch and I. Tamir, *J. Amer. Chem. Soc.* **91**, 2450 (1969).

molecular environment, and particularly to charge distribution. The method appears particularly valuable as a check of charge distributions calculated by MO methods and thus as an indication of the bonding in heterocycles. One of the four treatments already published⁶² is that for sydnone (see Section III,C, 5), but considerably more work is to be expected using this technique.

2. Ultraviolet Spectroscopy

Ultraviolet spectra have frequently been used as evidence for the aromaticity or lack of aromaticity of heterocycles, usually as supporting evidence. Most frequently, the spectrum is compared with some structurally analogous compound of known aromaticity, and the degree of similarity is taken as a qualitative, and often at least by implication as a semi-quantitative, indication of the aromaticity of the compound investigated.

Thus the strong similarity of the UV spectra of borazarenes to those of the corresponding carbocyclic compounds is considered evidence for considerable aromatic character of the former^{63, 64} (see also Section III,D, 10). The ultraviolet spectra of phosphabenzene⁶⁵, arsabenzene⁶⁶, and stibabenzene⁶⁶ also reflects the considerable delocalization in these rings (Sections III,D, 4 and 5).

By contrast the similarity of the UV of oxonin to that of cyclonona-tetraene is quoted as evidence⁶⁷ for lack of aromaticity (Section III,G) and UV was one criterion which led to the conclusion that 2-oxaazulen-6-one is only weakly aromatic⁶⁸ (Section III,H, 1).

3. Infrared Spectroscopy

Vibrational spectra reflect conjugation; if conjugation is absent, this precludes delocalization and hence aromaticity. This criterion has been applied, for example, to 1,4-dioxin,⁶⁹ which shows negligible aromaticity (Section III,D, 11); by contrast, the $\nu_{C=O}$ for several thiaazulenones⁷⁰

⁶² M. Barber, S. J. Broadbent, J. A. Connor, M. F. Guest, I. H. Hillier, and M. J. Puxley, *J. Chem. Soc. Perkin Trans. II*, 1517 (1972).

⁶³ M. J. S. Dewar, *Advan. Chem. Ser.* **42**, 227 (1964); *Progr. Boron Chem.* **1**, 235 (1964).

⁶⁴ M. J. S. Dewar, V. P. Kubba, and R. Pettit, *J. Chem. Soc.*, 3073 (1958).

⁶⁵ G. Märkl, *Angew. Chem. Int. Ed. Engl.* **5**, 846 (1966).

⁶⁶ A. J. Ashe, *J. Amer. Chem. Soc.* **93**, 6690 (1971).

⁶⁷ A. G. Anastassiou, S. W. Eachus, R. P. Cellura, and J. H. Gebrian, *Chem. Commun.*, 1133 (1970).

⁶⁸ M. J. Cook and E. J. Forbes, *Tetrahedron* **24**, 4501 (1968).

⁶⁹ J. E. Connett, J. A. Creighton, J. H. S. Green, and W. Kynaston, *Spectrochim. Acta* **22**, 1859 (1966).

⁷⁰ M. Winn and F. G. Bordwell, *J. Org. Chem.* **32**, 1610 (1967).

indicates an increased single-bond character consistent with ring delocalization.

4. Dipole Moments

The interpretation of dipole moments of aromatic compounds is fraught with difficulties because the measured moment is the sum of π -bond, σ -bond, and lone-pair moments. Thus although the large dipole moments of compounds such as pyridones clearly point to enhanced delocalization, quantitative treatment is not easy. Indeed in some cases the method is misleading, as with the borazabenzenes⁷¹ where σ - and π -bond moments may operate in opposite directions (Section III,D, 10).

D. THE MAGNETIC MODEL

1. Magnetic Anisotropy, Ring Currents, and Diamagnetic Susceptibility Exaltation

A discussion of the origins of the diamagnetic anisotropy in aromatic compounds is beyond the scope of the present review, but since the interpretation in terms of ring current⁷² has led to controversial discussions of aromaticity in heterocyclic compounds (following section), the ring current model is worth summarizing. The π -electrons of aromatic molecules are delocalized in extended circular orbitals above and below the plane of the ring, and therefore when a magnetic field is applied a large diamagnetic ring current is induced of much greater magnitude than the small circuit currents associated with the σ -electrons. The induced ring current produces a secondary magnetic field that opposes the applied field within the ring and reinforces it without, and is thus responsible, in part, for the observed deshielding of aromatic ring protons in the PMR spectrum.

The extent to which ring currents and local effects contribute to the anisotropy is a subject of discussion (see Pople,⁷³ Davies,⁷⁴ Dailey,⁷⁵ Musher⁷⁶). Recently Flygare *et al.*⁷⁷⁻⁸⁰ examined the rotational Zeeman

⁷¹ M. J. S. Dewar and R. Jones, *J. Amer. Chem. Soc.* **90**, 2137 (1968).

⁷² L. Pauling, *J. Chem. Phys.* **4**, 673 (1936).

⁷³ J. A. Pople, *J. Chem. Phys.* **41**, 2559 (1964).

⁷⁴ D. W. Davies, *Trans. Faraday Soc.* **57**, 2081 (1961).

⁷⁵ B. P. Dailey, *J. Chem. Phys.* **41**, 2304 (1964).

⁷⁶ J. I. Musher, *J. Chem. Phys.* **43**, 4081 (1965).

⁷⁷ R. C. Benson and W. H. Flygare, *J. Amer. Chem. Soc.* **92**, 7523 (1970).

⁷⁸ D. H. Sutter and W. H. Flygare, *J. Amer. Chem. Soc.* **91**, 4063, 6895 (1969).

⁷⁹ D. H. Sutter and W. H. Flygare, *Mol. Phys.* **16**, 153 (1969).

⁸⁰ D. H. Sutter, W. Hüttner, and W. H. Flygare, *J. Chem. Phys.* **50**, 2869 (1969).

effect for a variety of compounds from which evaluations of magnetic susceptibility anisotropies were made; studies on cyclopentadiene and isoprene⁷⁷ showed that local and nonlocal contributions are about equal in the former and it was suggested that this applies also to thiophene and pyrrole. Further anisotropy data⁷⁸ for furan, pyrrole, and thiophene were considered to demonstrate an increase in ring current in the series in the order given. More recently still, Flygare, Beak, *et al.*⁸¹ reported values for a parameter Δ_χ , the out-of-plane minus the average-in-plane molecular susceptibilities for the molecules benzene, furan, 2-pyrone, and 4-pyrone. The values of Δ_χ were separated into local and nonlocal contributions with the aid of values for localized groups obtained from nonaromatic compounds. The authors concluded from the apparent absence of nonlocal contributions in the pyrones that these are not aromatic compounds.

The concept of the closely related diamagnetic susceptibility exaltation was earlier discussed by Craig⁸² and Dauben *et al.*⁸³ These groups suggested that the difference, the exaltation, in the observed molar magnetic susceptibility χ_M and that calculated from atomic and bond contribution χ_M' , provides a useful criterion for assessing aromaticity. Dauben *et al.*⁸⁴ have recently provided an authoritative survey of the subject and a comprehensive compilation of exaltation values for benzenoid, nonbenzenoid, and pseudo-aromatics, aromatic cations, keto aromatics and heteroaromatics. Examples of the last series are provided here in Table VI. Some uncertainties arise in the calculations of χ_M' for five-membered heteroaromatics.

In a critical appraisal Jones⁸⁵ expressed the view that diamagnetic susceptibility exaltation provides a qualitative rather than a quantitative criterion for aromatic character. He argued that "the uncertainties in the value used for the diamagnetic constants for atoms and bonds, the need to use constitutive corrections⁸³ and in particular the uncertainties in the origin of the susceptibility which are clearly related to the problems of the ring current model, prevent the meaningful use of this phenomenon as a quantitative criterion."

⁸¹ R. C. Benson, C. L. Norris, W. H. Flygare, and P. Beak, *J. Amer. Chem. Soc.* **93**, 5591 (1971).

⁸² D. P. Craig, in "Non-benzenoid Aromatic Compounds" (D. Ginsburg, ed.), p. 1. Interscience, New York, 1959; "Theoretical Organic Chemistry," Kekule Symp., p. 20. Butterworth, London, 1959.

⁸³ H. J. Dauben, J. D. Wilson, and J. L. Laity, *J. Amer. Chem. Soc.* **90**, 811 (1968); **91**, 1991 (1969).

⁸⁴ H. J. Dauben, J. D. Wilson, and J. L. Laity, in "Non-benzenoid Aromatics" (J. P. Snyder, ed.), Vol. II, p. 167. Academic Press, New York, 1971.

⁸⁵ A. J. Jones, *Rev. Pure Appl. Chem.* **18**, 253 (1968).

TABLE VI
DIAMAGNETIC SUSCEPTIBILITY EXALTATION⁸⁴

Compound	χ_m (10^{-6} cm ³ mole ⁻¹)	χ_m'	Λ
Benzene	54.8	41.1	13.7
Pyridine	49.2	35.8	13.4
Pyrazine	37.6	30.5	7.1
Borazine	49.6	41.9	7.7
N-Ethylpyridone	74 \pm 1	67.3	7
Barbituric acid	53.8	55.4	-1.6
Thiophene	57.4	44.4	13.0
Pyrrole	47.6	37.4	10.2
Furan	43.1	34.2	8.9
1,3-Thiazole	50.6	38.3	12.3
Pyrazole	42.6	36.0	6.6
3,5-Dimethyloxazole	59.7	51.5	8.2
1,3,4-Thiadiazole	37.3	32.2	5.1
3,4-Dimethyl-1,2,5-oxadiazole	57.2	46.2	11.4
N-Phenylsydnone	88.1	77.1	11.0
Naphthalene	91.9	61.4	30.5
Quinoline	86.0	56.1	29.9
Isoquinoline	83.9	56.1	27.8
Indole	85.0	57.7	27.3
Anthracene	130.3	81.7	48.6
Acridine	123.3	76.4	46.9
Carbazole	117.4	78.0	39.4

2. Ring Currents and Proton Chemical Shifts

Elvidge and Jackman⁸⁶ suggested that the ring current deshielding of protons is sufficiently diagnostic of aromatic character for an aromatic compound to be defined as one which can sustain an induced ring current. They further suggested that the magnitude of the ring current might present a quantitative assessment of the aromaticity of a compound; their studies on the 2-pyridone and 2-pyridmethide rings led them to the conclusion that the former possesses about 35% of the aromaticity of benzene and the latter is probably nonaromatic.

Subsequently, Abraham *et al.*⁸⁷ compared the ring currents in furan and benzene from a consideration of the chemical shifts of the protons of these compounds with those in nonaromatic models (i.e., compounds which

⁸⁶ J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 859 (1961).

⁸⁷ R. J. Abraham, R. C. Sheppard, W. A. Thomas, and S. Turner, *Chem. Commun.*, 43 (1965).

could not sustain a ring current) and concluded that by the ring current criterion the aromaticity of these compounds is comparable. The variance with the accepted view of the degree of aromatic character of the heterocycle led them to conclude that ring current is not a simple function of the aromaticity of a molecule. Abraham's choice of nonaromatic models has been criticized by Elvidge⁸⁸ and using alternative models he derived an order of decreasing aromaticity of benzene, 1; thiophene, 0.75; pyrrole, 0.59; furan, 0.46. At about the same time De Jongh and Wynberg⁸⁹ using further chemical shift data obtained the order benzene, 1; thiophene, 0.77; furan, 0.60; while Davies⁹⁰ calculated the ring currents to be benzene, 1; pyrrole, 0.80; furan, 0.76; thiophene, 0.72. An attempt to estimate anisotropies of heteroaromatic compounds from molar Cotton-Mouton constants and polarizability and susceptibility data has led to the following relative values of π -ring currents: pyridine, 1.06; benzene, 1.0; thiophene, 0.79; furan, 0.57; pyrrole, 0.37.⁹¹

The difficulties in choosing a nonaromatic model in chemical shift studies have been discussed further by Abraham and Thomas,⁹² who also reasserted the view that the ring current criterion as a quantitative assessment of aromaticity is suspect, a view which has received some support elsewhere.⁹³⁻⁹⁵ However, in spite of the various difficulties and a criticism of the generality of the ring current criterion even for qualitative work,⁹⁶ the concept has been and remains for many authors a useful diagnostic test of aromaticity. Indeed PMR data has been cited in discussions of the aromatic character of an extensive number of compounds and the following examples serve to illustrate the range. Thus tellurophene,⁹⁷ the indole, benzothiophene, benzofuran series,⁹⁸ benzofurazan (4,5-benzo-2,1,3-oxadiazole),⁹⁹ indolizine,¹⁰⁰ cycl[3,2,2]azine,¹⁰¹ pyrazolo[1,2-a]pyrazole,¹⁰²

⁸⁸ J. A. Elvidge, *Chem. Commun.*, 160 (1965).

⁸⁹ H. A. P. De Jongh and H. Wynberg, *Tetrahedron* **21**, 515 (1965).

⁹⁰ D. W. Davies, *Chem. Commun.*, 258 (1965).

⁹¹ R. J. W. Le Fèvre and D. S. N. Murthy, *Aust. J. Chem.* **19**, 1321 (1966).

⁹² R. J. Abraham and W. A. Thomas, *J. Chem. Soc. B*, 127 (1966).

⁹³ L. M. Weinstock and P. I. Pollak, *Advan. Heterocycl. Chem.* **9**, 107 (1968).

⁹⁴ H. C. Smitherman and L. N. Ferguson, *Tetrahedron* **24**, 923 (1968).

⁹⁵ R. B. Mallion, *J. Mol. Spectrosc.* **35**, 491 (1970).

⁹⁶ D. E. Jung, *Tetrahedron* **25**, 129 (1969).

⁹⁷ W. Mack, *Angew. Chem. Int. Ed. Engl.* **5**, 896 (1966).

⁹⁸ J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, 590 (1963); 981 (1964).

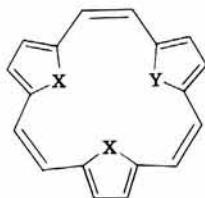
⁹⁹ B. Dischler and G. Englert, *Z. Naturforsch. A* **16**, 1180 (1961).

¹⁰⁰ P. J. Black, M. L. Heffernan, L. M. Jackman, Q. N. Porter, and G. R. Underwood, *Aust. J. Chem.* **17**, 1128 (1964).

¹⁰¹ V. Boekelheide, F. Gerson, E. Heilbronner, and D. Meuche, *Helv. Chim. Acta* **46**, 1951 (1963).

¹⁰² T. W. G. Solomons and C. F. Voigt, *J. Amer. Chem. Soc.* **88**, 1992 (1966).

1,10-phenanthroline,¹⁰³ borazonaphthalene¹⁰⁴ and borazathienopyridine,¹⁰⁵ 7-methylpyrano[4,3-*b*]pyran-2,5-dione,¹⁰⁶ 3-phenyl-3-benzoborepin,¹⁰⁷ the heterocyclic analogs of pentalenyl dianion,^{47, 108-110} 1,6-oxido[10]-annulene,¹¹¹ 1,6-imino[10]annulene,¹¹² and 1,6:8,13-dioxido[14]-annulene¹¹³ are some systems regarded as having substantial π -electron delocalization by the chemical shift criterion. In the larger annulenes, chemical shift data have been used to ascribe aromatic character to the trioxide **14** (X = Y = O)^{114,115} and dioxide sulfide of [18]annulene (**14**,



(14)

X = O, Y = S),¹¹⁶ but polyene character to the corresponding oxide disulfide (**14**, X = S, Y = O)¹¹⁷ and trisulfide (**14**, X = Y = S).¹¹⁸ PMR data have also been cited as evidence for the comparable aromaticity of isothiazole and benzene¹¹⁹; the lower aromaticity of 4-pyrone compared to

¹⁰³ H. Rosenberger, M. Pettig, K. Madeja, and G. Klose, *Ber. Bunsenges. Phys. Chem.* **72**, 847 (1968).

¹⁰⁴ G. M. Badger, in "Aromatic Character and Aromaticity," p. 69. Cambridge Univ. Press, London and New York, 1969.

¹⁰⁵ S. Gronowitz and A. Bugge, *Acta Chem. Scand.* **19**, 1271 (1965); S. Gronowitz and J. Namtvedt, *ibid.* **21**, 2151 (1967).

¹⁰⁶ F. C. Cheng and S. F. Tan, *J. Chem. Soc. C*, 543 (1968).

¹⁰⁷ A. J. Leusink, W. Drenth, J. G. Noltes, and G. J. M. van der Kerk, *Tetrahedron Lett.*, 1263 (1967).

¹⁰⁸ H. Volz and B. Messner, *Tetrahedron Lett.*, 4111 (1969).

¹⁰⁹ T. S. Cantrell and B. L. Harrison, *Tetrahedron Lett.*, 4477 (1967).

¹¹⁰ T. S. Cantrell and B. L. Harrison, *Tetrahedron Lett.*, 1299 (1969).

¹¹¹ F. Sondheimer and A. Shani, *J. Amer. Chem. Soc.* **86**, 3168 (1964).

¹¹² E. Vogel, M. Biskup, W. Pretzer, and W. A. Böll, *Angew. Chem.* **76**, 785 (1964).

¹¹³ E. Vogel, M. Biskup, A. Vogel, and H. Günther, *Angew. Chem. Int. Ed. Engl.* **5**, 734 (1966).

¹¹⁴ G. M. Badger, J. A. Elix, and G. E. Lewis, *Aust. J. Chem.* **19**, 1221 (1966).

¹¹⁵ G. M. Badger, J. A. Elix, G. E. Lewis, U. P. Singh, and T. M. Spotswood, *Chem. Commun.*, 269 (1965).

¹¹⁶ G. M. Badger, G. E. Lewis, and U. P. Singh, *Aust. J. Chem.* **19**, 1461 (1966).

¹¹⁷ G. M. Badger, J. A. Elix, and G. E. Lewis, *Aust. J. Chem.* **19**, 257 (1966).

¹¹⁸ G. M. Badger, J. A. Elix, and G. E. Lewis, *Aust. J. Chem.* **18**, 70 (1965).

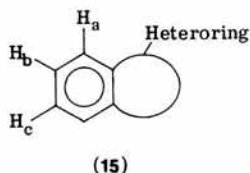
¹¹⁹ J. A. Elvidge, Personal communication to R. Slack and K. R. H. Woolridge, *Advan. Heterocycl. Chem.* **4**, 114 (1965).

4-thiothiapyrone¹²⁰ and of 2,1,3-benzothiadiazole compared to benzene and naphthalene¹²¹; a smaller ring current in furfural (formyl proton at δ 9.67) relative to that of benzaldehyde (9.96 ppm)¹²²; a small ring current in uric acid¹²³; and the absence of aromatic delocalization in the H-bonded form of 6-aminofulvene-2-aldimines.¹²⁴

Ring currents have been calculated for the porphine skeleton^{125, 126} and for purine, methylated purines, adenine, hypoxanthine, uric acid, imidazole, indole, and pteridine,¹²⁶ from which it was concluded that ring currents are higher for the hexagonal ring compared to the pentagonal ring.

3. Proton-Proton Coupling Constants and Bond Order

The variation of vicinal proton-proton coupling constants with bond order is a well-documented phenomenon and correlations have been reported for five-¹²⁷ and six-¹²⁸ membered ring aromatic systems. A plot of J_{vic} against bond orders for various halothiophenes gives a near straight line correlation.¹²⁹ Vicinal coupling constants are therefore potentially useful for providing evidence for bond fixation or delocalization and have frequently been used for this purpose, e.g., Günther¹³⁰ and references therein. In particular, Günther¹³⁰ has suggested that for heteroaromatic rings fused to a benzenoid ring (15) the ratio of the *ortho* couplings $J_{bc}:J_{ab}$



may serve as a guide to π -electron delocalization. The ratio should be 1

¹²⁰ J. Jonas, W. Derbyshire, and H. S. Gutowsky, *J. Phys. Chem.* **69**, 1 (1965).

¹²¹ E. I. Fedin, Z. V. Todries, and L. S. Egros, *Khim. Geterotsikl. Soedin.*, 297 (1967); *Chem. Abstr.* **68**, 2858p (1968).

¹²² R. E. Klinck and J. B. Stothers, *Can. J. Chem.* **44**, 45 (1966).

¹²³ C. Geissner-Prettre and B. Pullman, *C. R. Acad. Sci. Ser. D* **261**, 2521 (1965).

¹²⁴ U. Müller-Westerhoff, *J. Amer. Chem. Soc.* **92**, 4849 (1970).

¹²⁵ G. Hazato, *Proc. Int. Symp. Mol. Struct. Spectrosc.* (D 217) 1962; *Chem. Abstr.* **61**, 2597d (1964).

¹²⁶ C. Geissner-Prettre and B. Pullman, *C. R. Acad. Sci. Ser. D* **268**, 1115 (1969).

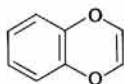
¹²⁷ W. B. Smith, W. H. Watson, and S. Chiranjeevi, *J. Amer. Chem. Soc.* **89**, 1438 (1967).

¹²⁸ N. Jonathan, S. Gordon, and B. P. Dailey, *J. Chem. Phys.* **36**, 2443 (1962).

¹²⁹ J. M. Read, C. T. Mathis, and J. H. Goldstein, *Spectrochim. Acta* **21**, 85 (1965).

¹³⁰ H. Günther, *Tetrahedron Lett.*, 2967 (1967).

for complete π -bond equivalence and 0.5 for complete localization (for an application see Section III,C, 6). Vicinal couplings, particularly in a heteroaromatic ring, may be strongly influenced by ring angles and the inductive and other effects of heteroatoms (see Abraham and Pachler¹³¹ for a discussion) and therefore some care should be observed in their application. Thus $J_{23} = 6$ Hz in 4-pyrone and 10 Hz in 4-thiapyrone, whereas the latter is regarded to be the more aromatic by the ring current criterion.¹²⁰ However, a sensible choice of compounds used for comparative purposes can overcome these problems, e.g., the nonaromaticity of 1,4-benzodioxin (16) was demonstrated by the similarity of J_{23} with J_{23} in dioxene (17).¹³²



(16)



(17)

4. The Dilution Shift Parameter

The dilution shift $\Delta\delta_1$ defined as the difference between the chemical shift of aromatic protons in the pure liquid and that in an infinitely dilute solution in nonpolar solvents, is inversely proportional to the molar volume (V_m) of the solute and directly proportional to the difference in the magnetic susceptibilities parallel and perpendicular to the axis of the ring.^{133, 134} On this basis Khetrapal and co-workers have argued^{134, 135} that the percentage aromaticity (A) of a system relative to benzene (100%) can be calculated from the expression:

$$A = \frac{(\Delta\delta_1 V_m) \text{ for ring protons of the compound } (\times 100)}{(\Delta\delta_1 V_m) \text{ for benzene protons}}$$

From data obtained in CCl_4 the following percentage aromaticities have been derived: pyridine, 61 ± 7 ; furan, 42 ± 5 ; thiophene, 69 ± 11 , and these have been discussed and compared with estimates from other methods. In extensions the aromaticities of various substituted thiophenes

¹³¹ R. J. Abraham and K. G. R. Pachler, *Mol. Phys.* **7**, 165 (1963–1964).

¹³² A. R. Katritzky, M. Kingsland, M. N. Rudd, M. J. Sewell, and R. D. Topsom, *Aust. J. Chem.* **20**, 1773 (1967).

¹³³ A. D. Buckingham, T. P. Shaefer, and W. G. Sneider, *J. Chem. Phys.* **32**, 1227 (1960).

¹³⁴ C. R. Kanekar, G. Govil, C. L. Khetrapal, and M. M. Dhingra, *Proc. Indian Acad. Sci. Sect. A* **64**, 315 (1966).

¹³⁵ S. S. Dharmatti, M. M. Dhingra, G. Govil, and C. L. Khetrapal, *Proc. Nucl. Phys. Solid State Phys. Symp.*, 8th, Part B, p. 410 (1964); *Chem. Abstr.* **66**, 60548g (1967).

were determined¹³⁶ and measurements in solutions of benzene have been recommended¹³⁷ in which the shifts of the benzene solvent peak are determined. The value for pyridine seems to be particularly low and this may be due to the apparent neglect of effects which might arise from the presence of lone pairs of electrons.

The same group¹³⁸ has applied the method to fluorobenzenes, and Bertelli and Golino¹³⁹ have independently used solvent shift criteria for an examination of π -electron delocalization in various nonbenzenoid aromatic hydrocarbons.

5. The Solvent Shift Parameter S

Anet and Schenck¹⁴⁰ have suggested that the magnitude of the strong shifts induced by aromatic solvents in the PMR spectra of dipolar molecules may provide information about molecular magnetic isotropies of these solvents. The chemical shift difference between acetonitrile and cyclohexane (internal reference) in solvent X is $\Delta\sigma_X = \Delta\sigma_{\text{gas}} + \Delta\sigma_{\text{medium}}$. Referring all $\Delta\sigma_X$ values to $\Delta\sigma_{\text{cyclohexane}}$, defined as the observed chemical shift between acetonitrile and cyclohexane in neat cyclohexane, the relative solvent shifts S , equal to $\Delta\sigma_X - \Delta\sigma_{\text{cyclohexane}}$, may be obtained. For aromatic compounds, S values are large: here the dominant effect is the preferential location of the acetonitrile dipole above the plane of the ring where π -electron density and diamagnetic shielding are greatest. In practice, the association constants of acetonitrile with the aromatic ring will affect the magnitude of S , though for hydrocarbon solvents these may be regarded as being sufficiently similar to make S a measure of the anisotropy experienced. S for benzene is 1.00 ppm whereas S values for olefins are near to zero.

S values decrease in the order pyrrole, thiophene, and furan. For pyrrole, the S value of 0.82 is higher than expected (anisotropy $\chi = 0.71$; benzene = 1) whereas for furan the S value of 0.42 is lower than expected, cf. $\chi = 0.65$. For pyrrole the result is interpreted in terms of a larger association constant, and for furan, the involvement of association at the periphery resulting in a deshielding contribution.

The approach has been extended to the heteronins (Section III,G) and the results (Table VII) suggest that, by the present criterion, oxonin is

¹³⁶ M. M. Dhingra, G. Govil, C. R. Kanekar, and C. L. Khetrpal, *Proc. Indian Acad. Sci. Sect. A* **65**, 203 (1967).

¹³⁷ C. R. Kanekar and C. L. Khetrpal, *Curr. Sci.* **36**, 67 (1967); *Chem. Abstr.* **67**, 2666d (1967).

¹³⁸ C. L. Khetrpal and M. M. Dhingra, *Curr. Sci.* **36**, 572 (1967).

¹³⁹ D. J. Bertelli and C. Golino, *J. Org. Chem.* **30**, 368 (1965).

¹⁴⁰ F. A. L. Anet and G. E. Schenck, *J. Amer. Chem. Soc.* **93**, 556 (1971).

TABLE VII
SOLVENT SHIFT PARAMETER S

Compound	Temp. (°C)	S	Ref.
Benzene	33	+1	140
Pyrrole	33	+0.82	140
Furan	33	+0.42	140
Cyclononatetraene	0	-0.05	398
Oxonin	0	-0.07	398
1 <i>H</i> -Azonine	0	+1.35	398
<i>N</i> -Methylazonine	0	+0.34	398

mildly antiaromatic whereas 1*H*-azonine is strongly aromatic. It has been suggested that steric hindrance renders *N*-methylazonine nonplanar and this accounts for the reduced S value for this compound. Such a large decrease in the S value on replacing N-H by N-Me would seem to imply a nonlinear relationship between aromatic character and S .

6. ^{13}C NMR Spectrometry

Theoretical considerations^{141,142} show that there is some correlation between π -electron density and ^{13}C shifts. Lauterbur's extension¹⁴³ of his empirical approach to the heterocycles pyridine, pyridazine, pyrimidine, *s*-triazine, and *s*-tetrazine and some of their methyl derivatives shows that the ^{13}C shieldings of the ring carbon atoms are approximately proportional to π -electron density. Page *et al.*¹⁴⁴ examined the five-membered ring heterocycles and suggested that aromatic character is implied for furan, pyrrole, and thiophene from the similarity of the ^{13}C shifts with those of the benzenoid aromatics; they inferred, however, that σ -bond effects preclude analysis of a simple relationship between chemical shifts and π -electron density. Others¹⁴⁵ were unable to find any such correlation for various substituted pyrazoles. By contrast Weigert and Roberts¹⁴⁶ found a linear relationship between $2p_z$ atomic population and ^{13}C shifts in the five-membered ring heterocycles containing one, two, three and four nitrogen atoms, and Lynch¹⁴⁷ reports a linear correlation between both ^{13}C and

¹⁴¹ M. Karplus and J. A. Pople, *J. Chem. Phys.* **38**, 2803 (1963).

¹⁴² J. A. Pople, *Mol. Phys.* **7**, 301 (1963-1964).

¹⁴³ P. C. Lauterbur, *J. Chem. Phys.* **43**, 360 (1965).

¹⁴⁴ T. F. Page, T. Alger, and D. M. Grant, *J. Amer. Chem. Soc.* **87**, 5333 (1965).

¹⁴⁵ R. G. Rees and M. J. Green, *J. Chem. Soc. B*, 387 (1968).

¹⁴⁶ F. J. Weigert and J. D. Roberts, *J. Amer. Chem. Soc.* **90**, 3543 (1968).

¹⁴⁷ B. M. Lynch, *Chem. Commun.*, 1337 (1968).

^1H chemical shifts and simple Hückel π -electron densities in pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, and tetrazole. The latter results, according to the author, suggest that ^{13}C and ^1H shifts in these azoles are determined by the same factors, namely, the π -electron densities. Goldstein and Reddy¹⁴⁸ pointed out that since ^{13}C -H coupling constants are relatively insensitive to anisotropy, medium effects and other factors which complicate the interpretation of proton chemical shifts, then departures from a correlation between $J^{13}\text{C-H}$ and δ could allow a measure of these perturbing factors. By this criterion the anisotropy effect for thiophene has been estimated¹⁴⁸ to be half the magnitude of that of benzene, but interpretation of the data for furan and pyrrole is complicated by local effects associated with the heteroatom.

7. The Faraday Effect

The Faraday effect is the rotation of the plane of polarization of light by transparent substances when placed in a magnetic field. The rotation is an additive property and may be calculated for a compound from the known rotation of the bonds. Isolated carbon-carbon multiple bonds make large contributions to the observed rotation but in compounds containing conjugated bonds there is an exaltation over the calculated rotation.¹⁴⁹ Labarre and Crasnier,¹⁵⁰ on the basis of a ring current definition of aromaticity, proposed the following magneto-optical criteria for aromaticity of compounds:

(a) Unsubstituted cyclic planar molecules that are characterized by a large magnetic rotation exaltation E_{Ar} .

(b) Substitution for hydrogen by fluorine or chlorine atoms should sharply decrease the E_{Ar} value whereas substitution by an amino group should increase it.

(c) The molecular magnetic rotation of the molecule should not remain constant when the molecule is diluted in an inert solvent.

These criteria have been applied in an assessment of the aromaticity of some borazines and boroxines,¹⁵¹ and to provide the following order of decreasing aromaticity: pyridine 1-oxide, pyridine, benzene¹⁵²; and

¹⁴⁸ J. H. Goldstein and G. S. Reddy, *J. Chem. Phys.* **36**, 2644 (1962).

¹⁴⁹ J.-F. Labarre, *Ann. Chim. (Paris)* **8**, 45 (1963).

¹⁵⁰ J.-F. Labarre and F. Crasnier, *J. Chim. Phys.* **64**, 1664 (1967).

¹⁵¹ J.-F. Labarre, M. Graffeuil, and F. Gallais, *J. Chim. Phys.* **65**, 638 (1968); J.-F. Labarre, M. Graffeuil, J. P. Funcher, M. Padeloup, and J. P. Lawrent, *Theor. Chim. Acta* **11**, 423 (1968); M. Graffeuil and J.-F. Labarre, *J. Chim. Phys.* **66**, 177 (1969).

¹⁵² J. Devanneaux and J.-F. Labarre, *J. Chim. Phys.* **66**, 1174 (1969).

thiophene, pyrrole, furan,¹⁵³ in which series furan has very low aromatic character. The difficulties arising from the comparison of compounds belonging to different symmetry groups (e.g., benzene, thiazole) have been demonstrated by the same group.¹⁵³

Labarre and co-workers^{154,155} and another group¹⁵⁶ have subsequently reported that criterion (c) is invalid and this has been withdrawn. It was shown that the concentration dependence of the molar magnetic rotation of an aromatic molecule does not correlate with diamagnetic effects of an induced ring current, but rather it is associated with the concentration-dependent change of the internal field of the solute. Consequently it does not reflect the aromaticity of the compound.

Labarre, in a more recent paper,¹⁵⁵ has questioned the exact meaning of the term "aromaticity" and in particular its relationship to ring current effects.

E. THE REACTIVITY MODEL

There have been many discussions of the aromaticity of heterocycles based upon experimental observations of the mode and ease of reaction toward various reagents, particularly electrophiles. Conclusions so drawn are inevitably qualitative and fall short in that reactivity is a function of transition-state stability as well as ground-state stability. Recently, however, two groups have explored theoretically the energetics of hypothetical addition and substitution pathways of unsaturated molecules. Kruszewski and Krygowski³⁵ have introduced the KK index which is simply proportional to the π -electron energy (calculated by the HMO method) that a molecule would lose as a result of an addition reaction. Compounds with $KK > 3.00$ are classified by the authors as being aromatic; thus benzene is calculated as 3.55; pyridine, 3.53; and 1,3,5-hexatriene, 2.5. The KK index follows approximately the same order as Julg's A_1 values (Section II,B) and Zahradník's³⁴ specific delocalization energy, DE_{sp} (Section II,A, 3, a). In a subsequent paper¹⁵⁷ the calculations are extended and include thiophene, pyrrole, and furan, and a scale of decreasing aromaticity, in the order thiophene, benzene, furan, pyrrole is obtained.

¹⁵³ J. Devanneaux and J.-F. Labarre, *J. Chim. Phys.* **66**, 1780 (1969).

¹⁵⁴ J.-F. Labarre, R. Moezi, and J.-F. Kéruszorè, *J. Chim. Phys.* **66**, 2018 (1969).

¹⁵⁵ J.-F. Labarre, *Bull. Soc. Chim. Fr.*, 2463 (1970).

¹⁵⁶ K. Bauer, E. Eberhardt, H. Falk, G. Haller, and H. Lehner, *Monatsh. Chem.* **101**, 469 (1970).

¹⁵⁷ T. M. Krygowski, *Tetrahedron Lett.*, 1311 (1970).

A more sophisticated approach by Dixon¹⁵⁸ derives an index A ; a large value for A is associated with chemical inertness or preferred substitution over addition. However, at the present time the method has not been applied to heteroaromatics.

F. MISCELLANEOUS CRITERIA

1. Aromaticity Constants

Balaban and Simon¹⁵⁹ have argued that an index based on the relative electrophilicity and nucleophilicity of a ring compared with benzene is a useful means of expressing in numerical terms the aromaticity of a ring system. The authors derive an aromaticity constant K from a summation of k values for each ring position, where k is an expression of the tendency of the atom to release or attract π -electrons from the delocalized π -cloud and is defined by

$$k = \left(0.478 \frac{Z^*}{r} - 1.01 - \mu \right) 100$$

where

$$Z^* = Z - 0.85\mu_K - 0.525\mu_{L,n} - 0.175\mu_{L,b}$$

and Z is the nuclear charge; Z^* , the effective charge; r , the covalent radius; μ_K , the number of electrons in the K shell; $\mu_{L,n}$, the number of nonbonding L electrons; $\mu_{L,b}$, number of bonding L electrons; and μ , number of π -electrons.

A representative selection of K values is listed in Table VIII. The equation for K is such that the value of K for benzene is 0 and the authors suggest that compounds with $K > |200|$ are likely to be too unstable to be isolated.

It is clear from this treatment that the method does not attempt to assign a specific amount of "aromaticity" to a compound but rather to correlate numerically the chemical behavior of the compound relative to benzene. The authors point out that, in devising K values for particular atoms, factors such as strain, positional isomerism, and the existence of mesoionic structures are neglected. It is also suggested that in making predictions about stability of structures, possible formation of stable decomposition products must be taken into account. Thus hypothetical

¹⁵⁸ W. T. Dixon, *J. Chem. Soc. B*, 612 (1970).

¹⁵⁹ A. T. Balaban and Z. Simon, *Tetrahedron* **18**, 315 (1962).

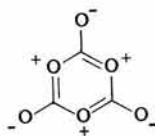
TABLE VIII
AROMATICITY CONSTANTS¹⁶⁹ *K*

Compound	<i>K</i>
Benzene	0
Pyridine	+23
Pyridinium perchlorate	+74
Prylium perchlorate	+97
Pyrone	+57
2-Pyridone	+34
"2-Hydroxypyridine"	+16
Cyclopentadienide	-100
Pyrrole	-26
Sodium pyrrolate	-77
Furan	-3
Tropylium	+100
Borepin	+28

structures such as the hexazine (18) and carbon dioxide trimer (19) have *K* values of only 138 and 171, respectively.



(18)



(19)

2. Stability Index *P*

Zahradník *et al.*¹⁶⁰ have combined a set of parameters which may be regarded as "aromaticity indices" into the *stability index*. The approach is more comprehensive than that of Balaban, but as the authors point out it is obviously difficult to assess the relative importance of the selected indices. Those included are the specific delocalization energy DE_{sp} ³⁴ (Section II,A,3,a) related to the extent of π -electron delocalization, Δq the difference between the maximum and minimum π -electron density in the molecule (related to the reactivity toward nucleophilic and electrophilic reagents; see the preceding section), the free valence *F* (related to radical reactivity) and the radical super-delocalizability *S_r* (related to radical reactivity, oxidizability, and reducibility).

¹⁶⁰ R. Zahradník, J. Michl, and J. Pancíř, *Tetrahedron* **22**, 1355 (1966).

From a study of hydrocarbons the authors define the stability index P as

$$P = 273 \frac{(\text{DE}_{\text{sp}} - 0.2796)(0.552 - \Delta q)(0.586 - F)}{S_r}$$

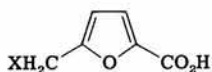
No values of P for heteroaromatics are quoted but a qualitative application to sulfur heteroaromatics is considered elsewhere¹⁶¹ within a discussion of the uncertainties of this type of approach.

3. Coefficients of Influence

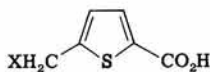
Berezin¹⁶² has argued that vibrational force constants are a quantitative characteristic of the properties of the electron shells of molecules and has proposed that the coefficients of influence (where the matrix of the coefficients of influence is the inverse of that of the force constants) may serve as a quantitative criterion for aromaticity. The coefficients of influence for benzene, pyridine, pyrazine, s-triazine, and s-tetrazine have been calculated from the force constants of the molecules and the sum of the diagonal coefficients of influence of all six internal ring angles and seem to increase as Balaban's K values (Section II,F, 1) for these compounds decrease.

4. Sensitivity to Substituent Effects

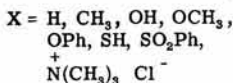
Exner and Simon¹⁶³ have proposed that the transmission of the inductive effect through an aromatic ring may serve as a measure of the mobility of the π -electrons and thus also as an indirect measure of the aromatic character of the skeleton. From an examination of the two series **20** and **21** the effects of substituents on the dissociation constants



(20)



(21)



of thiophene-2-carboxylic acid and 2-furoic acid are compared and contrasted with similar results obtained earlier¹⁶⁴ for substituted benzoic acids.

¹⁶¹ R. Zahradník, *Advan. Heterocycl. Chem.* **5**, 1 (1965).

¹⁶² V. I. Berezin, *Dokl. Phys. Chem.* **155**, 305 (1964).

¹⁶³ O. Exner and W. Simon, *Collect. Czech. Chem. Commun.* **29**, 2016 (1964).

¹⁶⁴ O. Exner and J. Jonáš, *Collect. Czech. Chem. Commun.* **27**, 2296 (1962).

The authors concluded that the "sensitivity to substituent effects" increases in the order benzene, thiophene, furan and they reason that the aromatic character increases in the reverse order.

Extension^{165,166} to pyrrole- and selenophene-2-carboxylic acids gives a sequence of sensitivity in the order pyrrole, furan, selenophene, thiophene, benzene, the same order as that observed by Tirouflet *et al.*¹⁶⁷ in the polarographic reduction of nitro derivatives of these rings. A different sequence, however, which correlates better with "ground state aromatic character", *viz.*, furan, pyrrole, thiophene, benzene, has been observed in the gas-phase ionization process,¹⁶⁸ but results for electrophilic substitution appear to be anomalous.¹⁶⁹

G. SUMMARY

The criteria for aromaticity described in the preceding sections have been used rather unevenly and are of varying reliability and utility. A brief critical summary and comparison of the various methods is now attempted.

The electronic model is almost invariably invoked: IR and UV spectra are easy to obtain and are required for proper characterization—but the information obtained is highly qualitative. Certain aspects of the magnetic model are also easy to apply, and high hopes have been held for the magnetic model as a criterion of aromaticity. Indeed, it does provide useful qualitative criteria, but chemical shifts and coupling constants are sensitive to other structural and environmental influences so as to hinder quantitative application.

The geometric model is probably well based, but is difficult to apply, needing highly accurate structural parameters. The reactivity model and the other miscellaneous methods have not achieved wide usage. Energetic criteria remain the most promising: although the combustion and hydrogenation methods developed for carbocycles are not easily applied, other methods are now available. MO calculations are making great progress, but still need experimental confirmation.

The number of indices aimed at quantifying aromatic character un-

¹⁶⁵ F. Fringuelli, G. Marino, and G. Savelli, *Tetrahedron* **25**, 5815 (1969).

¹⁶⁶ T. A. Melent'eva, L. V. Kazanskaya, and V. M. Berezovskii, *Dokl. Chem.* **175**, 624 (1967).

¹⁶⁷ J. Tirouflet, *Congr. Int. Quin. Pure Appl.*, **15th** **1**, 1 (1957); in "Advances in Polarography" (I. S. Longmuir, ed.), p. 740. Pergamon, Oxford, 1960; J. Tirouflet and J.-P. Chane, *C. R. Acad. Sci.* **245**, 80 (1957); **243**, 500 (1956).

¹⁶⁸ P. Linda, G. Marino, and S. Pignataro, *J. Chem. Soc. B*, 1585 (1971).

¹⁶⁹ S. Clementi and G. Marino, *Chem. Commun.*, 1642 (1970).

doubtedly emphasizes the positive interest and effort which this subject attracts. It must, however, be stated that a number of these indices introduce a quantitative description of a property associated with "aromatic" compounds which may or may not be obviously related to the chemists' notions of aromaticity itself. Some indices introduce modifications and even new definitions of aromaticity. It is indeed a subject for debate as to whether an increase in the number of such indices leads to a corresponding increase in the understanding of aromatic character. Readers may well incline to the view that while the work undoubtedly stimulates interest and in many cases a greater comprehension of electronic and physicochemical properties, discussions of aromaticity based on the development of studies on the thermodynamic stability and geometry of aromatic compounds may in the long run prove to be the more enlightening for the organic chemist.

III. The Aromaticity of Individual Heteroaromatic Rings

A. THREE-MEMBERED HETEROAROMATIC RING COMPOUNDS

Vol'pin *et al.*¹⁷⁰ have compiled an extensive list of structures isoelectronic with the cyclopropenium cation, for which stabilization of the two- π -electron systems is possible either by p - p - p or by p - p - d conjugation. A summary of the postulated systems is given in Table IX (see also Balaban¹⁷¹). Reports of work directed towards the preparation of these rings are rather few in number and studies on the aromaticity of the structures are correspondingly scarce. A lack of stability may be implied for some systems from their propensity to elude preparation, and attempts to synthesize the germirene (22) and silirene (23) rings exemplify some disappointments in this area. The preparations of both ring systems were initially claimed by Vol'pin and his co-workers^{170, 172} but subsequent studies on members of both series of products revealed that the compounds were in fact dimers,¹⁷³ for which the unsaturated six-membered ring structures

¹⁷⁰ M. E. Vol'pin, Yu. D. Koreshkov, V. G. Dulova, and D. N. Kursanov, *Tetrahedron* **18**, 107 (1962).












¹⁷¹ A. T. Balaban, *Stud. Cercet. Chim.* **7**, 257 (1959).

¹⁷² M. E. Vol'pin, V. G. Dulova, and D. N. Kursanov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 649 (1963); L. A. Leites, V. G. Dulova, and M. E. Vol'pin, *ibid.*, 653 (1963).

¹⁷³ F. Johnson and R. S. Gohlke, *Tetrahedron Lett.*, 1291 (1962); M. E. Vol'pin, Yu. T. Struchkov, L. V. Vilkov, V. S. Mastuykov, V. G. Dulova, and D. N. Kursanov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1909 (1963); R. West and R. E. Bailey, *J. Amer. Chem. Soc.* **85**, 2871 (1963).

TABLE IX

POSTULATED THREE-MEMBERED HETEROAROMATIC COMPOUNDS¹⁷⁰

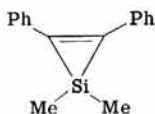
Structure	Heteroatoms (X =)
	B, Al, Ga, In, Tl, P, As, Sb.
	(Si, Ge, Sn) ^a
	Si, Ge, Sn, Pb
	(N, P, As, Sb) ^a
	P, As, Sb
	P, As, Sb
	S, Se, Te
	S, Se, Te
	S, Se, Te
	S, Se, Te
	Halogen

^a Series expected to be highly unstable.

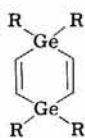
(24) and (25) have either been proposed or proven. Attempts to prepare triphenylborirene (26) were equally disappointing in that only products which may have been derived from it were obtained.¹⁷⁴



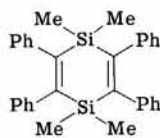
(22)



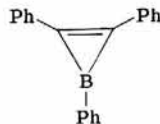
(23)



(24)

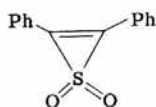


(25)

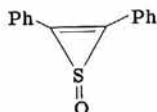


(26)

Recent work, however, on some of the sulfur-containing rings has proved more profitable. Both the sulfone (27)¹⁷⁵ and sulfoxide (28)¹⁷⁶

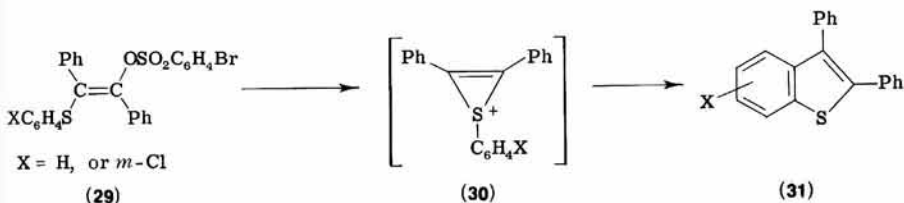


(27)



(28)

have been isolated but as yet the compounds have not been examined under the criteria discussed in the earlier sections. The sulfoxide is more stable than the sulfone, which in turn shows an enhanced stability over the saturated analog. Compelling evidence has also been presented¹⁷⁷ for the intermediacy of the thiirenium cation (30) in the unimolecular conversion of the β -arythiovinyl benzenesulfonates (29) into benzo[*b*]thiophene derivatives (31). Nonempirical SCF-MO calculations¹⁷⁸ show that the



thiirenium ion (32) is substantially (65.9 kcal mole⁻¹) more stable than

¹⁷⁴ J. J. Eisch and L. J. Gonsior, *J. Organometal. Chem.* **8**, 57 (1967).

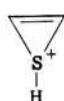
¹⁷⁵ L. A. Carpino, L. V. McAdams, R. H. Rynbrandt, and J. W. Spiewak, *J. Amer. Chem. Soc.* **93**, 476 (1971).

¹⁷⁶ L. A. Carpino and Hung-Wen Chen, *J. Amer. Chem. Soc.* **93**, 785 (1971).

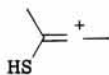
¹⁷⁷ G. Capozzi, G. Melloni, G. Modena, and U. Tonellato, *Chem. Commun.*, 1520 (1969).

¹⁷⁸ A. S. Denes, I. G. Csizmadia, and G. Modena, *J. Chem. Soc. D*, 8 (1972).

the linear β -thiovinyl cation (33). A calculation on azacyclopropenyl [azinium ion, 34] has given a value of 1.58 β for its DE¹⁷⁹



(32)



(33)



(34)

By contrast, special instability (antiaromaticity) is to be expected for the three-membered rings containing a heteroatom with lone pairs of electrons. The thiirene¹⁶¹ and oxirene¹⁸⁰ ring systems have been subjects of calculations which indicate zero DE, while Clark¹⁸¹ and Dewar *et al.*¹³ have predicted that the latter should have negative resonance energy. The 1*H*-azirine (2-azirine) nucleus 35 is similarly referred to as being antiaromatic^{13, 181-183} and has been observed to rearrange to the non-aromatic 1-azirine system 36.¹⁸³



(35)



(36)

B. FOUR-MEMBERED HETEROAROMATIC RING COMPOUNDS

Either two- π - or six- π -electron systems could in principle be developed over a four-membered ring but there appears to be a paucity of published work in this field. Krespan and co-workers¹⁸⁴ have described the preparation of 3,4-bis(trifluoromethyl)-1,2-dithietene (37) from the reaction of hexafluoro-2-butyne and sulfur; 37 is thermally stable, but is converted into its dimer on treatment with triethylamine. Equilibration studies, however, revealed that the monomer is the more stable species at 200°. More recently a nitrogen analog, the Δ^3 -1,2-diazetine (38) has been described and it does not appear to sustain a diamagnetic ring current. This, together with the slow cleavage of the nitrogen-nitrogen bond even

¹⁷⁹ G. R. Harvey and K. W. Ratts, *J. Org. Chem.* **31**, 3907 (1966).

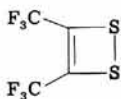
¹⁸⁰ R. N. McDonald and P. A. Schwab, *J. Amer. Chem. Soc.* **86**, 4866 (1964).

¹⁸¹ D. T. Clark, *Theor. Chim. Acta* **15**, 225 (1969).

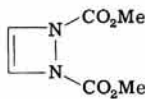
¹⁸² F. W. Fowler and A. Hassner, *J. Amer. Chem. Soc.* **90**, 2875 (1968).

¹⁸³ D. J. Anderson, T. L. Gilchrist, and C. W. Rees, *Chem. Commun.*, 147 (1969).

¹⁸⁴ C. G. Krespan, *J. Amer. Chem. Soc.* **83**, 3434 (1961); C. G. Krespan, B. C. McKusick, and T. L. Cairns, *ibid.* **82**, 1515 (1960).



(37)



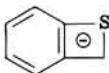
(38)

at room temperature, appears to rule out any substantial six- π -electron delocalization.¹⁸⁵

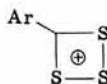
Potential six- π -electron anions containing sulfur which have been considered are the thieto anion **39**¹⁸⁶ and its benzofused analog **40**.¹⁸⁷ Both were predicted to be unstable, however, and have not, to our knowledge, been prepared. Steric strain and unfavorable energy characteristics have also been predicted¹⁶¹ for the trithietanylium ion. An attempt, however, to prepare a derivative (**41**)¹⁸⁸ gave a compound which may well have



(39)



(40)



(41)

the required ring system, but the possibility that the compound isolated was a dimer could not be excluded.

C. FIVE-MEMBERED HETEROAROMATIC RING COMPOUNDS

1. Thiophene, Pyrrole, Furan, and Analogs

Properties of various compounds discussed in this section from which evidence for or against aromatic character can be drawn have been surveyed in recent reviews. Marino¹⁸⁹ has discussed the aromaticity of furan, pyrrole, and thiophene, Jones¹⁹⁰ has extensively surveyed the physicochemical properties of pyrrole, and Magdesieva⁵⁸ those of selenophene. Earlier reviews are available on the properties of furan,¹⁹¹ pyrrole,¹⁹² and thiophene.¹⁹³ To avoid unnecessary duplication only a summary of the extensive data is presented here.

¹⁸⁵ E. E. Nunn and R. N. Warrener, *J. Chem. Soc. D*, 818 (1972).

¹⁸⁶ D. C. Dittmer and M. E. Christy, *J. Amer. Chem. Soc.* **84**, 399 (1962).

¹⁸⁷ R. Zahradník and C. Párkányi, *Collect. Czech. Chem. Commun.* **30**, 3016 (1965).

¹⁸⁸ E. Campaine, M. Pragnell, and F. Haaf, *J. Heterocycl. Chem.* **5**, 141 (1968).

¹⁸⁹ G. Marino, *Advan. Heterocycl. Chem.* **13**, 235 (1971).

¹⁹⁰ R. A. Jones, *Advan. Heterocycl. Chem.* **11**, 383 (1970).

¹⁹¹ P. Bosshard and C. H. Eugster, *Advan. Heterocycl. Chem.* **7**, 377 (1966).

¹⁹² K. Schofield, "Heteroaromatic Nitrogen Compounds: Pyrroles and Pyridines," Butterworths, London, 1967.

¹⁹³ S. Gronowitz, *Advan. Heterocycl. Chem.* **1**, 1 (1963).

A consideration of the results of molecular structural determinations of furan,¹⁹⁴ pyrrole,¹⁹⁵ thiophene,¹⁹⁶ and selenophene^{197,198} shows that bond alternation as exemplified by the ratio (R) of the C-2-C-3 to C-3-C-4 bond lengths decreases in the order, furan ($R = 0.950$), selenophene ($R = 0.956$), pyrrole ($R = 0.959$), and thiophene ($R = 0.964$). Whether this corresponds to an aromaticity scale,¹⁸⁹ considering that the bond angles at the heteroatom are widely divergent, is a matter for debate. The X-ray structure determination¹⁹⁹ of 1,2,5-triphenylphosphole is discussed later.

Of the ring systems considered in this section, thiophene, pyrrole, and furan have received the most extensive study and much of this has been of a comparative nature. As can be seen from Table X, these compounds have been compared by nearly all of the criteria by which aromaticity may be assessed. Although there are one or two discrepancies in the order of aromatic character as estimated by these criteria, the general conclusion to be drawn is that aromatic character decreases in the order benzene, thiophene, pyrrole, and furan. This order is also supported from studies of the Faraday effect,¹⁵³ although the KK index (Section II,E) reverses the position in the order of thiophene and benzene.¹⁵⁷

Comparison of the chemical shifts of the formyl protons in benzaldehyde and furfural suggests that the latter has the smaller ring current,¹²² and the difference between the chemical shifts of the protons at C-2 and C-3 in thiophene,²⁰⁰ selenophene,²⁰¹ and furan²⁰¹ has been cited⁵⁸ as evidence for the greater aromatic character of thiophene. PMR data suggest that tellurophene sustains a ring current.⁹⁷ The effect of 1-substituents on the ring current in the pyrrole ring has been discussed, and it was concluded that there is no evidence that the substituent causes any appreciable variation.²⁰² Proton chemical shift data for 2,5-dimethyl-1-phenylarsole are comparable to the data for the corresponding phosphole²⁰³; discussion

¹⁹⁴ B. Bak, D. Christensen, W. B. Dixon, L. Hansen-Nygaard, J. Rastrup-Andersen, and M. Schottländer, *J. Mol. Spectrosc.* **9**, 124 (1962).

¹⁹⁵ P. Bak, D. Christensen, L. Hansen-Nygaard, and J. Rastrup-Andersen, *J. Chem. Phys.* **24**, 720 (1956).

¹⁹⁶ B. Bak, D. Christensen, L. Hansen-Nygaard, and J. Rastrup-Andersen, *J. Mol. Spectrosc.* **7**, 58 (1961).

¹⁹⁷ N. M. Pozdeev, O. B. Akulinin, A. A. Shapkin, and N. N. Magdesieva, *Dokl. Akad. Nauk. SSSR* **185**, 384 (1969).

¹⁹⁸ R. D. Brown, F. R. Burden, and P. D. Godfrey, *J. Mol. Spectrosc.* **25**, 415 (1968).

¹⁹⁹ W. P. Ozbirn, R. A. Jacobson, and J. C. Clardy, *Chem. Commun.*, 1062 (1971).

²⁰⁰ R. A. Hoffman and S. Gronowitz, *Ark. Kemi* **15**, 45 (1960).

²⁰¹ T. Isobe, *Bull. Chem. Res. Inst. Non-Aqueous Solutions, Tohoku Univ.* **9**, 115 (1960).

²⁰² R. A. Jones, T. McL. Spotswood, and P. Cheuychit, *Tetrahedron* **23**, 4469 (1967).

²⁰³ G. Märkl and H. Hauptmann, *Tetrahedron Lett.*, 3257 (1968).

TABLE X

DATA FOR THIOPHENE, PYRROLE, AND FURAN

	Section ^a	Ref.	Units	Thiophene	Pyrrrole	Furan
ERE (Thermochemical data)	A, 1	6a-e	kcal mole ⁻¹	24.1-31	14-31 ^b	15.8-23
Conjugation energy	A, 1, a	7, 6h	kcal mole ⁻¹	16, 20	15	8
Dewar resonance energy	A, 2	10, 13	kcal mole ⁻¹	6.5	5.3	4.3
Aromaticity indexes, A_1	B	52	rel. benzene-1	0.93	0.91	0.87
		55	rel. benzene-1	0.67	0.38	0.06
Diamagnetic susceptibility exaltation	D, 1	84	$\times 10^{-6}$ cm ³ mole ⁻¹	13.0	10.2	8.9
Chemical shifts (a) α -protons	D, 1, 2	c	δ in ppm	7.19	6.62	7.40
(b) β -protons		c	δ in ppm	7.04	6.05	6.30
Anisotropy	D, 1	140	rel. benzene-1	—	0.71	0.65
Ring current susceptibility	D, 1, 2	90	rel. benzene-1	0.55	0.53	0.49
Ring currents (a) calculated	D, 1, 2	90	rel. benzene-1	0.72	0.80	0.76
(b) via chem. shifts	D, 2	88	rel. benzene-1	0.75	0.59	0.46
(c) via chem. shifts	D, 2	89	rel. benzene-1	(0.90)	(0.67)	(0.52)
(d) via Cotton-Mouton studies	D, 2	91	rel. benzene-1	—	0.71	0.65
Dilution shift approach	D, 4	134, 136	rel. benzene-1	0.79	0.37	0.57
Solvent shift S'	D, 1	140	rel. benzene-1	0.69	—	0.42
Aromaticity constants K	F, 1	159	rel. benzene-1	—	0.82	0.42
			rel. benzene-1	—	-26	-3

^a All Section references in Section II.^b Cf. 27 kcal mole⁻¹ obtained from basicity measurements.^{50,51}^c L. M. Jackman and S. Sternhell, in "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed., p. 209. Pergamon Press, New York, 1969.

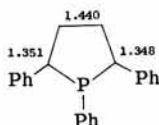
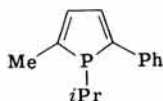


Fig. 1. Bond lengths of 1,2,5-triphenylphosphole.¹⁹⁹

of PMR data for phospholes appears below. ¹³C Chemical shifts of thiophene, pyrrole, and furan and some methyl derivatives have been reported, but conclusions regarding the aromaticity of the rings are difficult to draw; however, it was suggested that the anisotropy effect in thiophene is about half that in benzene.¹⁴⁸

The sensitivity to substituent effects (Section II,F, 4), which has been regarded by some authors to be an indirect measure of aromatic character, gives orders of aromaticity^{163, 168, 204} benzene, thiophene, pyrrole, furan and also thiophene, selenophene, furan, pyrrole.

The question of aromaticity of the phosphole ring system centers closely on whether the phosphorus atom is sp^2 -hybridized, allowing $2p + 4p$ π -electron delocalization or sp^3 -hybridized, where hybridization minimizes overlap of the lone pair with the π -system. A recent X-ray crystallographic study¹⁹⁹ on 1,2,5-triphenylphosphole has shown that the phosphorus atom indeed approaches sp^3 hybridization and that the heterocyclic ring itself is nonplanar. The bond lengths, which are similar to those of butadiene, are shown in Fig. 1; the results therefore imply a lack of substantial aromatic character. Mislow *et al.*, a little earlier, investigated the barriers to phosphorus inversion in 1-isopropyl-2-methyl-5-phenylphosphole (**42**)²⁰⁵



(42)

and subsequently extended their study to a range of other phospholes and benzophospholes.²⁰⁶ They found that the barriers to inversion were substantially lower than the barriers observed in saturated phosphorus compounds. Thus the barrier to inversion of the P atom in **42** is of the order of 16 kcal mole⁻¹ (some 23 kcal mole⁻¹ lower than in model systems²⁰⁵), and they associated this with the increased delocalization

²⁰⁴ D. Spinelli, G. Guanti, and C. Dell'Erba, *Ric. Sci.* **38**, 1048 (1968); *Chem. Abstr.* **71**, 25195w (1969).

²⁰⁵ W. Egan, R. Tang, G. Zon, and K. Mislow, *J. Amer. Chem. Soc.* **92**, 1442 (1970).

²⁰⁶ W. Egan, R. Tang, G. Zon, and K. Mislow, *J. Amer. Chem. Soc.* **93**, 6205 (1971).

(aromaticity) of the planar transition state. Studies on benzophospholes showed a decreased aromaticity (of the planar form) relative to that of the planar monocyclic ring. Brown²⁰⁷ had earlier calculated a DE of 1.49 β for the planar phosphole ring (cf. pyrrole 1.57 β and arsole 1.45 β) using the HMO method.

Earlier thermochemical data²⁰⁸ on the phosphole ring system may, however, be interpreted as showing that the ground state also has some resonance stabilization, and the presence of an M⁺ peak in the mass spectrum of 1-methylphosphole has been considered by Quin *et al.*⁴⁸ to typify heteroaromatic five-membered ring compounds. Various authors have cited PMR chemical shift data, e.g., of 2,5-dimethyl-1-phenylphosphole,²⁰⁹ 1-phenylphosphole,²¹⁰ and 1-methylphosphole⁴⁸ as possible evidence of aromatic character, but this does not seem particularly conclusive. Quin *et al.*⁴⁸ attributed the large value of $J_{23} = 7.24$ Hz in 1-methylphosphole (cf. pyrrole 2.4–3.1 Hz) to ring angle effects, but if, as now seems likely, the nonplanar ground state has little aromatic character, then an interpretation in terms of a high degree of double-bond character may be more appropriate. The UV spectral absorptions of 1-methylphosphole differ from those of divinylalkyl phosphine and resemble that of 1-methylpyrrole, but the latter resemblance may be coincidental. It should be noted that chemical evidence provides a somewhat divided view over the aromatic character of phospholes: see Campbell *et al.*²¹¹ and compare Farnham and Mislow.²¹²

In conclusion, it would appear that the available data on the simple five-membered heteroaromatic compounds suggest that the greatest aromaticity is to be associated with thiophene and that the aromaticity then falls along the series pyrrole, selenophene, furan with the ground state of the phosphole ring being probably nonaromatic.

2. Thiophene Oxides and Thiophenium Salts

The UV spectrum of thiophene-1,1-dioxide^{213,214} (43) is very different from that of thiophene and resembles, at least qualitatively, that of

²⁰⁷ D. A. Brown, *J. Chem. Soc.*, 929 (1962).

²⁰⁸ A. F. Bedford, D. M. Heinekey, I. T. Millar, and C. T. Mortimer, *J. Chem. Soc.*, 2932 (1962).

²⁰⁹ G. Märkl and R. Potthast, *Angew. Chem. Int. Ed. Engl.* **6**, 86 (1967).

²¹⁰ G. Märkl and R. Potthast, *Tetrahedron Lett.*, 1755 (1968).

²¹¹ I. G. M. Campbell, R. C. Cookson, M. B. Hocking and A. N. Hughes, *J. Chem. Soc.*, 2184 (1965); A. N. Hughes and S. Uabooukul, *Tetrahedron* **24**, 3437 (1968).

²¹² W. B. Farnham and K. Mislow, *J. Chem. Soc. D*, 469 (1972).

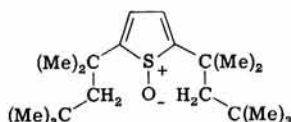
²¹³ W. J. Bailey and E. W. Cummins, *J. Amer. Chem. Soc.* **76**, 1932 (1954).

²¹⁴ M. Procházko, *Collect. Czech. Chem. Commun.* **30**, 1158 (1965).

cyclopentadiene. A further dissimilarity between the spectra of thiophene and its 1-monoxide argues for reduced aromaticity of the latter system also. From the NMR spectrum of 2,5-di-*tert*-octylthiophene-1-oxide²¹⁵ (44); which shows nonequivalence of the methylene protons at -10° but equivalence at 60° , the sulfoxide group was concluded to be pyramidal with a barrier to interconversion of ~ 15 kcal mole⁻¹, a barrier some 20 kcal mole⁻¹ lower than in other sulfoxides. As in the case of phospholes²⁰⁵ (preceding section) it can be argued that this lowering of the inversion barrier is due to an increase in the aromaticity as the ring becomes planar. It has also been pointed out,²¹⁵ however, that it could equally be derived from the relief of antiaromatic destabilization associated with the pyramidal form.

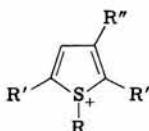


(43)



(44)

Thiophenium (45) and benzothiophenium salts have also been investigated recently by physical methods. The NMR spectra show that the ring protons absorb in the aromatic region,^{216,217} but clearly a separation of the ring current effect from the effect of the positive charge is difficult. The salts appear to possess a pyramidal sulfur atom,²¹⁷ which argues for a decrease in the aromaticity of these compounds relative to thiophene. The UV spectra of the salts are different from the spectra of the parent rings and resemble more closely the spectra of thiophene 1-oxide and thiophene 1,1-dioxide, which has been cited²¹⁷ as further evidence for reduced aromaticity of the salts.



R = Me or Et
R' = H or Me
R'' = H or Me

(45)

²¹⁵ W. L. Mock, *J. Amer. Chem. Soc.* **92**, 7610 (1970).

²¹⁶ G. C. Brumlik, A. I. Kosak, and R. Pitcher, *J. Amer. Chem. Soc.* **86**, 5360 (1964).

²¹⁷ R. M. Acheson and D. R. Harrison, *J. Chem. Soc. C*, 1764 (1970).

3. Imidazole, Pyrazole, Thiazole, Isothiazole, and Oxazole

ERE and "conjugation energy" data are available for both imidazole and pyrazole but the range of values is extremely wide (Table II). The trend suggests that pyrazole is more aromatic than both imidazole and pyrrole. Recent LCAO-SCF calculations on various azoles,²¹⁸ however, lead to the conclusion that the stability of azoles decreases on increasing substitution of nitrogen atoms for carbon atoms, with the stabilities of pyrazole and imidazole being comparable. A crystal structure investigation of imidazole at -150° showed that the ring is completely planar within the limits of the experimental error, with the following bond lengths: N-1-C-2 1.349 Å; C-2-N-3 1.326 Å; N-3-C-4 1.378 Å; C-4-C-5 1.358 Å; and C-5-N-1 1.369 Å.²¹⁹ An estimate of the relative importance of all reasonable resonance canonicals showed that the ring is well represented by the neutral structure representation. PMR shifts for imidazoles,²²⁰ pyrazoles,²²¹ and pyrrole²²² are comparable and ^{13}C NMR spectral data for imidazole have been advanced as evidence for the existence of an appreciable ring current anisotropy.¹⁴⁸

Analysis of the microwave spectrum of thiazole has shown that the structure is very close to an average of the structure of thiophene and 1,3,4-thiadiazole.²²³ The ring protons of thiazoles and the methyl protons in methylthiazoles^{92, 224, 225} are deshielded relative to signals from the corresponding imidazoles. PMR data for a large number of isothiazoles have been presented, including those for the parent compound.^{226, 227} The latter are said to be in good agreement with an early Hückel MO π -electron density calculation²²⁸ and Elvidge¹¹⁹ has interpreted the NMR data as evidence that the ring has the same degree of aromatic character as benzene.

PMR data for 4-methyloxazole have been compared with those of 4-methylthiazole but no conclusions were drawn about the ring currents, although the data clearly show that the ring protons in each are de-

²¹⁸ M. Roche and L. Pujol, *J. Chim. Phys.* **68**, 465 (1971).

²¹⁹ S. Martinez-Carrera, *Acta Crystallogr.* **20**, 783 (1966).

²²⁰ G. S. Reddy, R. T. Hobgood, and J. H. Goldstein, *J. Amer. Chem. Soc.* **84**, 336 (1962); A. Mannschreck, W. Seitz, and H. A. Staab, *Ber. Bunsenges. Phys. Chem.* **67**, 470 (1963).

²²¹ I. L. Finar and E. F. Mooney, *Spectrochim. Acta* **20**, 1269 (1964).

²²² N. Joop and H. Zimmermann, *Ber. Bunsenges. Phys. Chem.* **66**, 440 (1962).

²²³ L. Nygaard, E. Asmussen, J. H. Høg, R. C. Maheshwari, C. H. Nielsen, I. B. Petersen, J. Rastrup-Andersen, and G. O. Sorensen, *J. Mol. Structure* **8**, 225 (1971).

²²⁴ T. Schaefer and W. G. Schneider, *J. Chem. Phys.* **32**, 1224 (1960).

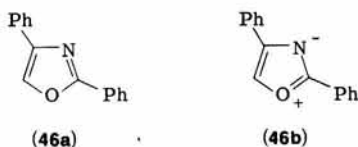
²²⁵ A. Taurins and W. G. Schneider, *Can. J. Chem.* **38**, 1237 (1960).

²²⁶ H. A. Staab and A. Mannschreck, *Chem. Ber.* **98**, 1111 (1965).

²²⁷ R. C. Anderson, *J. Heterocycl. Chem.* **1**, 279 (1964).

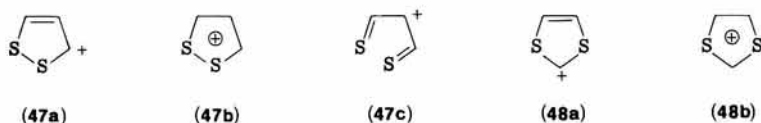
²²⁸ A. Adams and R. Slack, *J. Chem. Soc.*, 3061 (1959).

shielded.²²⁹ In a comprehensive study of a range of oxazoles, Brown and Ghosh²³⁰ also reported NMR data but avoided drawing conclusions from them, and instead they based a discussion of resonance stabilization on pK_a and UV spectral data. They argued that the feeble basicity of oxazole (pK_a 0.8) relative to 1-methylimidazole (pK_a 7.44) and thiazole (pK_a 2.44) demonstrates that any delocalization of the oxygen lone pair, which they suggest would have a base-strengthening effect on the N atom, is not extensive. Their UV spectrum of 2,4-diphenyloxazole (46) is an approximate superimposition of the 2- and 4-phenyloxazole absorptions, which rather elegantly suggests that the charge-separated canonical form **46b** is unimportant. They conclude that the ring may best be regarded as a "diene."



4. Diheterolium Cation and Related Compounds

The aromatic character of 1,2-dithiolium and 1,3-dithiolium cations (**47**, **48**) has been discussed in an earlier review in this series.²³¹ In that survey these compounds were described as being iso- π -electronic with tropylium ion, from which they may be formally derived by replacing double bonds by sulfur atoms. Various calculations and structural data were cited to demonstrate that the rings are stabilized by π -electron delocalization.



The possibility that the 1,2-dithiolium cations are stabilized by no bond resonance structures of type **47c** has been considered and discussed²³² (see also Lozac'h²³³) in the light of interesting findings such as those of Hordvik,²³⁴ who showed that the internal pair of sulfur atoms in **49** is

²²⁹ P. Haake and W. B. Miller, *J. Amer. Chem. Soc.* **85**, 4044 (1963).

²³⁰ D. J. Brown and P. B. Ghosh, *J. Chem. Soc. (B)*, 270 (1969).

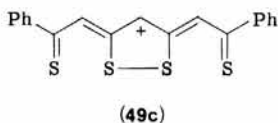
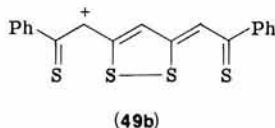
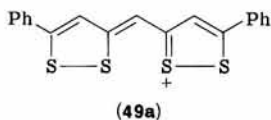
²³¹ H. Prinzbach and E. Futterer, *Advan. Heterocycl. Chem.* **7**, 39 (1966).

²³² E. Klingsberg, *J. Heterocycl. Chem.* **3**, 243 (1966).

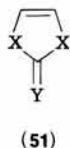
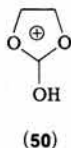
²³³ N. Lozac'h, *Advan. Heterocycl. Chem.* **13**, 161 (1971).

²³⁴ A. Hordvik, *Acta Chem. Scand.* **19**, 1253 (1965).

separated by only 3.00–3.10 Å, which is indicative of partial bonding between this pair, i.e., participation of canonical forms **49b** and **49c**.



The NMR spectrum of 2-hydroxy-1,3-dioxolium cation (**50**), obtained by dissolving vinylene carbonate (**51**, X = Y = O) in a sulfur dioxide solution of 1:1 fluorosulfonic acid and antimony pentafluoride, has been discussed by Olah and White.²³⁵ The signals for the ring protons in the cation are shifted downfield relative to the olefinic protons in the neutral compound to an extent which was associated with the presence of a significant ring current in the cation. That the starting vinylene carbonate fulfills the conditions for aromaticity was pointed out earlier by Balaban,¹⁷¹ and this same author has recently reviewed²³⁶ the scant chemical and physical data available for this series and its analogs.



1,2-Dithiole-3-ones and 1,2-dithiole-3-thiones appear to be nearly planar and Brown *et al.*²³⁷ examined the PMR spectra of a large number of compounds in this series, but it was not possible to make any firm conclusion concerning the aromaticity of the systems, although it seems likely that the order of the C-4–C-5 bond is less than 2. More recently²³⁸ linear correla-

²³⁵ G. A. Olah and A. M. White, *J. Amer. Chem. Soc.* **90**, 1884 (1968).

²³⁶ A. T. Balaban, *Rev. Roum. Chim.* **14**, 1323 (1969).

²³⁷ R. F. C. Brown, I. D. Rae, and S. Sternhell, *Aust. J. Chem.* **18**, 1211 (1965).

²³⁸ D. M. McKinnon and T. Schaefer, *Can. J. Chem.* **49**, 89 (1971).

tions have been found between two bond proton- ^{13}C couplings and *cisoid* proton-proton couplings in a series of ethylenic compounds and again for some aromatic compounds: the compounds **51**, $\text{X} = \text{Y} = \text{O}$; **51**, $\text{X} = \text{Y} = \text{S}$; and **51**, $\text{X} = \text{S}$, $\text{Y} = \text{O}$, more closely follow the correlation for the olefins than that followed by benzene, furan, and thiophene.

5. Compounds Containing Three Heteroatoms

Trends become obscured as the number of heteroatoms in the ring becomes larger. Assessment of the strong downfield shift of ring protons in terms of ring currents for systems where the ring is electron-deficient is particularly difficult, and this problem has been discussed in some detail by Weinstock and Pollak.⁹³ What does appear to be clear is that the aromatic character is rather critically dependent upon the position of the heteroatoms in the ring, and second, as was already apparent in Section III.C, 3 that oxygenated compounds have marked diene character. 1,2,4-Triazole has been subject to various ERE determinations which have given values ranging between 20.0 and 49.2 kcal mole⁻¹ (Table II). LCAO-SCF calculations,²¹⁸ however, suggest that the ring is substantially less stable than the diazoles but more stable than tetrazole. It is of some interest that a good linear relationship between π -electron density for triazoles and diazoles (as calculated by the simple MO method) and ^{13}C chemical shifts appears to exist.¹⁴⁷

The existing evidence for aromatic character in 1,3,4-thiadiazole (**52**) and 1,2,5-thiadiazole (**53**) is compatible with the conclusion that both these compounds may well be regarded as aromatic. In particular, Bak *et al.*⁵⁹ analyzed the microwave spectrum of 1,3,4-thiadiazole (**52**) and, after appraising previous structural determinations of thiophene (**54**),¹⁹⁶ 1,2,5-thiadiazole (**53**),²³⁹ and 1,2,5-oxadiazole (**55**),²⁴⁰ derived the following order of decreasing aromaticity based on bond lengths: **53**, **54**, **52**, **55**, **56**. The data for 1,2,5-oxadiazole²⁴⁰ obtained from an

**(52)****(53)****(54)****(55)****(56)**

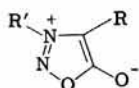
analysis of the microwave spectrum demonstrate that the molecule is planar with a $\text{C}=\text{N}$ bond length of 1.300 Å, intermediate between that of

²³⁹ S. V. Dobyys and L. Pierce, *J. Amer. Chem. Soc.* **85**, 3553 (1963).

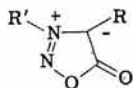
²⁴⁰ E. Saegbarth and A. P. Cox, *J. Chem. Phys.* **43**, 166 (1965).

formaldoxime (1.270 Å) and pyridine (1.340 Å),²⁴¹ and is suggestive of a high degree of "diene" character. Subsequently Bak *et al.*⁵⁹ compared the data with those obtained by Scharpen and Laurie²⁴² for cyclopentadiene and concluded that 1,2,5-oxadiazole has some small degree of aromatic character. Derivatives of 1,2,4-oxadiazole (56) have been investigated by Moussebois and Oth.²⁴³ They examined UV and NMR data and concluded that there is no evidence of resonance interaction between the oxygen atom and the rest of the ring.

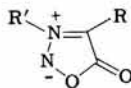
Perhaps the most studied of oxadiazoles are the sydnones and some views on their aromatic character are summarized here. For detailed reviews the reader is referred to Ohta and Kato,²⁴⁴ Bloor *et al.*²⁴⁵ Stewart,²⁴⁶ and Baker and Ollis.²⁴⁷ The sydnones may be represented by structures 57a-d, of which the mesoionic structure 57a most clearly implies an aromatic sextet.



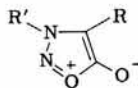
(57a)



(57b)



(57c)



(57d)

Baker and Ollis²⁴⁷ have advanced UV data as evidence for aromatic character, while a mean value for the diamagnetic susceptibility exaltation for *N*-phenyl sydnone of $11.0 \times 10^{-6} \text{ cm}^3 \text{ mole}^{-1}$ is comparable with the corresponding values for pyrrole (10.2×10^{-6}), furan (8.9×10^{-6}), and thiophene (13.0×10^{-6})⁸⁴ (cf. Matsunaga²⁴⁸). NMR data have been cited, however, as both "the strongest proof of the aromaticity of sydnones²⁴⁹" and "difficult to reconcile with the mesoionic formulation."²⁴⁶ An X-ray analysis²⁵⁰ of 3-*p*-bromophenylsydnone (57, R = H; R' = *p*-bromophenyl) has demonstrated that the ring is essentially planar with the O-N bond and O-1-C-5 bond not significantly different from normal single-bond distances. Together with an exocyclic O-C-5 bond length of

²⁴¹ B. Bak, L. Hansen-Nygaard, and J. Rastrup-Andersen, *J. Mol. Spectrosc.* **2**, 361 (1958).

²⁴² L. H. Scharpen and V. W. Laurie, *J. Chem. Phys.* **43**, 2765 (1965).

²⁴³ C. Moussebois and J. F. M. Oth, *Helv. Chim. Acta* **47**, 942 (1964).

²⁴⁴ M. Ohta and H. Kato, in "Nonbenzenoid Aromatics" (J. P. Snyder, ed.), Vol. 1, p. 117. Academic Press, New York, London, 1969.

²⁴⁵ J. E. Bloor, B. R. Gilson, and F. P. Billingsley, *Theor. Chim. Acta* **12**, 360 (1968).

²⁴⁶ F. H. C. Stewart, *Chem. Rev.* **64**, 129 (1964).

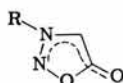
²⁴⁷ W. Baker and W. D. Ollis, *Quart. Rev.* **11**, 15 (1957).

²⁴⁸ Y. Matsunaga, *Bull. Chem. Soc. Jap.* **30**, 227 (1957).

²⁴⁹ K. D. Lawson, W. S. Brey, and L. B. Kier, *J. Amer. Chem. Soc.* **86**, 463 (1964).

²⁵⁰ H. Bärnighausen, F. Jellinek, J. Munnik, and A. Vos, *Acta Crystallogr.* **16**, 471 (1963).

1.20, which corresponds to a double bond, these data would argue against the more obviously aromatic formulations **57a** and **57b**. More recently, two sets^{245, 251} of MO calculations have been reported which further suggest that the formulation of the compounds as resonance-stabilized azomethine-imine structures is the most appropriate, and a combined MO-ESCA investigation⁶² has been interpreted in terms of structure **58**.



(58)

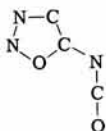
Earlier a Russian group calculated,²⁵² using the simple LCAO-MO method, the electronic skeleton of sydnone (**59**), sydnoneimine (**60**), the acyl derivative (**61**) of the latter, and derived cations of types **62** and **63**, and they concluded that the electron delocalization increased in the series **60**, **62**, **59**, **61**, and **63**.



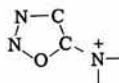
(59)



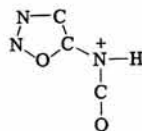
(60)



(61)



(62)



(63)

6. Some Benzo Derivatives

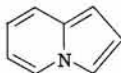
ERE determinations of indole have given results ranging from 41.8 to 57.6 kcal mole⁻¹.²⁵³ Dewar *et al.*^{10, 12} have calculated Dewar resonance energies for various benzo-fused compounds and obtained the following orders of decreasing resonance energy: benzo[*b*]thiophene, 24.8 kcal mole⁻¹; indole, 23.8 kcal mole⁻¹; benzo[*b*]furan, 20.3 kcal mole⁻¹. However,

²⁵¹ K. Sundaram and W. P. Purcell, *Int. J. Quant. Chem.* **2**, 145 (1968).

²⁵² D. A. Bochvar and A. A. Bagatur'yants, *Russ. J. Phys. Chem.* **39**, 867 (1965).

²⁵³ H. Zimmermann and H. Geisenfelder, *Z. Electrochem.* **65**, 368 (1961). (See also Cook *et al.*⁵⁰ and Lloyd⁵¹ for application of basicity data.)

in the isomeric series the order is somewhat different in that isoindole is the most aromatic: isoindole, 11.6 kcal mole⁻¹; benzo[*c*]thiophene, 9.3 kcal mole⁻¹; benzo[*c*]furan, 2.4 kcal mole⁻¹. The ultraviolet absorption spectrum of indole has been compared²⁵⁴⁻²⁵⁶ with those of indene and indolizine (64), and the dissimilarity with that of indene argues for π -electron delocalization in indole, but this is not as complete as in the indolizine nucleus. As would be expected the UV spectrum of the *N,N*-dimethylindolium cation resembles that of indene. From an analysis²⁵⁷ of the PMR spectrum of benzo[*b*]thiophene it has been suggested that the ring current in the heterocyclic ring is not significantly less than that in benzene. It was further deduced from the *ortho* coupling constants that the partial bond fixation and aromaticity of the system are comparable to those of naphthalene. More surprising perhaps, in view of the calculations of the Dewar resonance energy, is that benzo[*c*]furan^{258, 259} exhibits an NMR spectrum which implies that the structure supports a strong diamagnetic ring current. Its UV spectrum²⁵⁹ appears to be similar to that of benzo[*c*]thiophene.²⁶⁰ Recent studies of the barriers to heteroatom inversion in the benzo[*b*]phosphole²⁶⁶ and benzo[*b*]arsole²⁶¹ structures (compare Section III, C, 1) imply $(4p + 2p)$ electron delocalization which is maximal in the planar transition state of the inversion process.



(64)

Introduction of a second nitrogen atom into the five-membered ring of indole causes an increase in the ERE of the system (Table II, Section II, A, 1). The series 1,3-benzoselenazole (65a), benzothiazole (65b), and benzoxazole (65c) has been investigated by PMR spectroscopy, and the deshielding effect on the methyl protons on changing the heteroatom X is in the opposite sense to the electronegativity of the atom.²⁶² The authors suggested that this may be explained qualitatively in terms of decreasing aromaticity in the order 65a, 65b, 65c.

²⁵⁴ J. M. Hollas, *Spectrochim. Acta* **19**, 753 (1963).

²⁵⁵ R. L. Hinman and J. Lang, *J. Org. Chem.* **29**, 1449 (1964).

²⁵⁶ S. F. Mason, *J. Chem. Soc.*, 3999 (1963).

²⁵⁷ K. D. Bartle, D. W. Jones, and R. S. Matthews, *Tetrahedron* **27**, 5177 (1971).

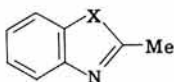
²⁵⁸ D. Wege, *Tetrahedron Lett.*, 2337 (1971).

²⁵⁹ R. N. Warrener, *J. Amer. Chem. Soc.* **93**, 2346 (1971).

²⁶⁰ R. Mayer, H. Kleinert, S. Richter, and K. Gewald, *J. Prakt. Chem.* **20**, 244 (1963).

²⁶¹ R. H. Bowman and K. Mislow, *J. Amer. Chem. Soc.* **94**, 2861 (1972).

²⁶² G. Di Modica, E. Barni, and A. Gasco, *J. Heterocycl. Chem.* **2**, 457 (1965).

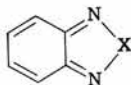


(65a) X = Se

(65b) X = S

(65c) X = O

Evidence for aromatic character of 2,1,3-benzoselenadiazole (**66a**), 2,1,3-benzothiadiazole (**66b**), and 2,1,3-benzoxadiazole (**66c**) has been discussed in a review article.²⁶³ The effect of the heteroatom X on the ring is similar to that in the previous system, thus a decreasing scale, **66a**, **66b**, **66c**, is again suggested. The reviewer emphasized the importance of resonance canonicals of type **67** for 2,1,3-benzoselena- and 2,1,3-benzo-

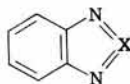


(66a) X = Se

(66b) X = S

(66c) X = O

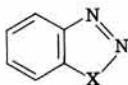
(66d) X = NMe



X = Se or S

(67)

thiadiazoles, although for the latter case the opposite view has been drawn from coupling constant data.²⁶⁴ A further analysis¹²¹ of the NMR spectrum of **66b** has led a Russian group to the conclusion that the compound is less aromatic than naphthalene. The same conclusion has been reached and extended to include 1,2,3-benzothiadiazole (**68a**), 2-methylbenzotriazole (**66d**), 1-methylbenzotriazole (**68b**), and 2,1,3-benzoxadiazole (**66c**) by Katritzky *et al.*²⁶⁴ who measured the *ortho* proton-proton coupling constants and, on assuming that these related to bond fixation and hence aromatic character, drew a scale of decreasing aromaticity: **68a**, **68b**, **66d**, **66b**, **66c**. The ratios of $J_{56}:J_{45}$ (Section II,D, 3) for these compounds are 0.859, 0.824, 0.781, 0.748, and 0.706, respectively.



(68a) X = S

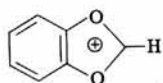
(68b) X = NMe

The NMR spectrum of the cationic species **69**, obtained in an SO₂ solution at -40°, shows the heterocyclic ring proton to be substantially

²⁶³ V. G. Pesin, *Russ. Chem. Rev.* **39**, 923 (1970).

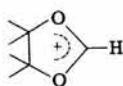
²⁶⁴ A. J. Boulton, P. J. Halls, and A. R. Katritzky, *Org. Magn. Res.* **1**, 311 (1969).

more deshielded than the corresponding proton in **70**, and this is considered evidence for a ring current in **69**²⁶⁵; cf. the data for the cation derived from vinylene carbonate (Section III,C, 4). Some degree of aromaticity has been suggested²³⁶ for *o*-phenylene carbonate (**71**) and the fulvene derivative (**72**). The UV spectrum of the cation derived from **71** has been interpreted in terms of π -electron delocalization.



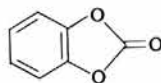
(69)

10.7 ppm

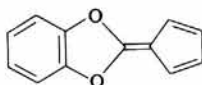


(70)

9.4 ppm



(71)



(72)

Dewar and co-workers have provided (Section II,A, 2) results of calculations of the Dewar resonance energy of some five-membered ring compounds fused to two benzene rings and the results demonstrate that a second benzene ring causes a further reduction in the aromaticity of the heterocyclic ring (see Table III). Values reported were dibenzofuran, 39.9; carbazole, 40.9; and dibenzothiophene, 44.6 kcal mole⁻¹. Frasca²⁶⁶ has examined the NMR spectra of the same three compounds together with that of fluorene and concludes that the ring current increases in the order fluorene, dibenzofuran, carbazole, dibenzothiophene. Basicity studies provide a value of 78 kcal mole⁻¹ for the ERE of carbazole.⁵⁰

D. SIX-MEMBERED HETEROAROMATIC RING COMPOUNDS

1. Pyridine

Pyridine is one of the most important heterocyclic analogs of benzene and its aromaticity has been examined under a large number of the quantitative criteria discussed in the earlier sections. Qualitatively, substitution of an sp^2 nitrogen atom for one of the sp^2 carbon atoms of benzene brings about a perturbation of the ideal hexagonal structure because of the different lengths of the C-N and C-C bonds, different bond angles about

²⁶⁵ H. Volz and G. Zimmermann, *Tetrahedron Lett.*, 3597 (1970).

²⁶⁶ A. R. Frasca, *An. Asoc. Quim. Argent.* **56**, 149 (1968); *Chem. Abstr.* **74**, 63625f (1971).

nitrogen and carbon, and the enhanced electronegativity of nitrogen over carbon. The precise geometry of the pyridine ring has been established from an examination of microwave spectra by Bak and co-workers.²⁴¹ The Copenhagen group reports bond lengths of 1.34 Å for the N-1-C-2 bond and 1.39 Å for both the C-2-C-3 and C-3-C-4 bonds. Bond angles in fact diverge from 120° by no more than 4°: \angle C-2-N-1-C-5 is 116° 50' and \angle N-1-C-2-C-3 is 123° 53'.

Empirical resonance energy (ERE) determinations have given values for pyridine ranging between 23 and 43 kcal mole⁻¹, Table I (see also Table XI). In four of the five papers cited a corresponding value for benzene is provided; the overall picture suggests that pyridine is the less aromatic. Similarly, the results of Cox's calculations⁷ of the conjugation energy (Section II,A, 1) are 19 kcal mole⁻¹ for pyridine and 22 kcal mole⁻¹ for benzene. The calculations of the Dewar resonance energy (Section II,A, 2), however, give values which are very similar: pyridine, 23.1 kcal mole⁻¹; benzene, 22.6 kcal mole⁻¹.¹³ A value of 2.1β for the delocalization energy (as defined in Section II,A, 3) has been reported from two early sets of MO calculations,^{21,22} but Davies²⁶⁷ subsequently reported a DE less than that of benzene (see Table XI). Zahradník and Koutecký²⁰ have noted that data for pyridine obey the equation $\text{ERE} = 15.8 \text{ DE}$. A large number of other MO calculations of various degrees of sophistication are available, e.g., Bene *et al.*,²⁶⁸ but discussion of these falls outside the scope of this review. In general, predicted properties have been similar to those found, and recently correlations between π -electron density and NMR parameters have been sought, e.g., Tokuhira and Fraenkel.²⁶⁹

The diamagnetic susceptibility exaltation of pyridine,⁸⁴ $13.4 \times 10^{-6} \text{ cm}^3 \text{ mole}^{-1}$, is fractionally lower than that for benzene (13.7×10^{-6}); estimation of aromaticity from proton chemical shift does not appear to have been attempted. By the dilution shift criterion (Section II,D, 4) a particularly low estimate of the aromaticity has been obtained, *viz.* 61% that of benzene.¹³⁷ On the other hand, the ratio of the π -ring current in pyridine to that in benzene has been calculated to be 1.06 from molecular susceptibility data,²⁷⁰ while from studies of the Faraday effect the order of decreasing aromaticity, pyridine *N*-oxide, pyridine, benzene, has been drawn.¹⁵²

²⁶⁷ D. W. Davies, *Trans. Faraday Soc.* **51**, 449 (1955).

²⁶⁸ J. D. Bene and H. H. Jaffé, *J. Chem. Phys.* **48**, 1807 (1968); I. Fischer-Hjalmars, *Pure Appl. Chem.* **11**, 571 (1965); K. Nishimoto and L. S. Forster, *Theor. Chim. Acta* **4**, 155 (1966).

²⁶⁹ T. Tokuhira and G. Fraenkel, *J. Amer. Chem. Soc.* **91**, 5005 (1969).

²⁷⁰ R. J. W. Le Fèvre and D. S. N. Murthy, *Aust. J. Chem.* **19**, 1321 (1966).

TABLE XI

CALCULATED DELOCALIZATION ENERGIES AND EXPERIMENTAL RESONANCE ENERGIES OF THE AZINES (KCAL MOLE⁻¹)

	MO method ^a		VB method ^b	Thermochemical data		Dewar resonance energy	
	Without overlap	With overlap		ERE values	Conj. energy ^c	d	e
Pyridine	40.8	39.4	37	23, ^{ed} 24.2, ^{eo} 27.9, ^{ea} 32, ^{ef} 43 ^{ec}	19	20.94	23.1
Pyridazine	39.9, ^f 42.4 ^g	36.8, ^f 41.2 ^g	22	12.3 ^{eo}	10	—	—
Pyrimidine	40.7	38.0	33	8.0 ^{eo}	18	20.20	17.1
Pyrazine	40.0	36.8	33	8.1, ^{eo} 24 ^{ef}	18	14.64	—
s-Triazine	40.5	36.6	29	—	—	—	—
vic-Triazine	—	—	25	—	—	—	—
as-Triazine	—	—	18	—	—	—	—
s-Tetrazine	—	—	20	—	—	—	—
vic-Tetrazine	—	—	10	—	—	—	—
as-Tetrazine	—	—	20	—	—	—	—
Pentazine	—	—	12	—	—	—	—

^a See Davies²⁶⁷; cf. Orgel *et al.*²¹ pyridine 2.1 β , pyrimidine 2.1 β , pyrimidine 2.2 β , pyrazine 2.2 β ; M. Simonetta, *J. Chim. Phys.* **49**, 69 (1952), pyridine 43, pyrazine 45. Values relative to a value of 41 for benzene.

^b A. Maccoll, *J. Chem. Soc.*, 670 (1946). Values relative to a value of 41 for benzene.

^c Cox⁷; benzene = 22.

^d Dewar *et al.*⁹; benzene = 20.04.

^e Dewar and Trinajstić¹³; benzene = 22.6.

^f With reference to the structure containing =N—N=.

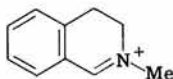
^g With reference to the structure containing —N=N—.

Kruszewski and Krygowski⁵⁵ have calculated the value of DE_{sp} (Section II,A,3a) to be 0.350 (benzene = 0.333) and the A_1 value (Section II,B) to be 1.0; Julg⁵⁵ reports a value for A of 0.97 (benzene = 1). At the same time they showed that the KK values (Section II,E) for both benzene and pyridine are 3.53. The decreased reactivity of pyridine (relative to benzene) towards electrophiles is reflected in the value of +23 for Balaban and Simon's aromaticity constant¹⁵⁹ (Section II,F, 1). Finally, Berezin¹⁶² has calculated the coefficient of influence (Section II,F, 3) of pyridine to be 1.987 (benzene 2.130) but the interpretation here seems somewhat difficult.

From the structural and electronic point of view, pyridine is the hetero-aromatic that is most similar to benzene and, as such, examination of the extent of agreement between the various estimates of aromaticity is of interest. By the stability criteria pyridine appears to have about the same as or somewhat less than the aromatic character of benzene. Of the other methods, with the exception of the dilution shift result, there is also an encouraging similarity of results and they reinforce the view that the two rings have comparable aromatic character. It is of interest that the ratio of the ring currents of pyridine and of benzene is also reported to be close to unity.²⁷⁰

2. Some Fused-Ring Derivatives of Pyridine

Determinations of the ERE of quinoline from thermochemical data have given results which range from 47.3 to 69 kcal mole⁻¹.^{49, 271, 272} There appear to be no corresponding estimates for isoquinoline, but a value of 48 ± 9 kcal mole⁻¹ has recently been deduced from a comparison of the equilibrium constants for pseudo-base formation of *N*-methylisoquinoline cation and its dihydro analog **73**.²⁷³ Comparison of these ERE values with those obtained for naphthalene (61–75 kcal mole⁻¹) shows that they parallel the somewhat lower resonance energy of pyridine relative to that of benzene.



(73)

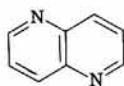
Recently, Dewar and his co-workers¹³ have provided, via calculations,

²⁷¹ L. Pauling and J. Sherman, *J. Chem. Phys.* **1**, 606 (1933).

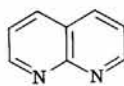
²⁷² G. W. Wheland, "Resonance in Organic Chemistry," p. 99. Wiley, New York, 1955.

²⁷³ R. D. Tack, Ph.D. Thesis, UEA, 1972; see also Cook *et al.*⁵⁰

values for the Dewar resonance energy (Section II,A, 2) of both quinoline and isoquinoline. The same value of 34.1 kcal mole⁻¹ was obtained for each system and is very similar to the result for naphthalene (33.6 kcal mole⁻¹). In the same paper values of 33.2 and 36.4 kcal mole⁻¹ were calculated for 1,5-naphthyridine (74) and 1,8-naphthyridine (75), respectively. The structures and other physicochemical properties of the latter two compounds together with a number of their isomers have recently been reviewed by Paudler and Kress.²⁷⁴ The same authors earlier calculated³² the values of DE for various members of this class of compounds and found that they all fell within the range of 3.76–3.85 β , which may be compared with the value of 3.68 β obtained for naphthalene.



(74)



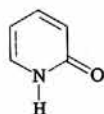
(75)

It is generally recognized that the fused-ring derivatives of pyridine sustain a ring current, but no attempts have apparently been made to evaluate it. Diamagnetic susceptibility exaltation measurements⁸⁴ give values for naphthalene of 30.5×10^{-6} , quinoline 29.9×10^{-6} , and isoquinoline 27.8×10^{-6} cm³ mole⁻¹.

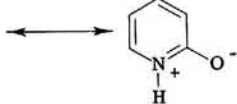
Although there are rather fewer quantitative estimates of the aromaticity of compounds discussed in this section compared with the number in the previous section, it is clear that the compounds rather closely resemble naphthalene in the same way in which pyridine resembles benzene.

3. Pyridones and Related Compounds

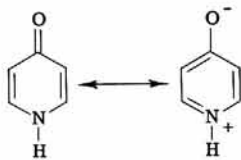
2- and 4-Pyridones (76) and (77) are potential six- π -electron ring systems, a feature which is more apparent when the charge-separated canonicals 76b and 77b are considered. Penfold²⁷⁵ has examined the X-ray



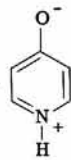
(76a)



(76b)



(77a)



(77b)

²⁷⁴ W. W. Paudler and T. J. Kress, *Advan. Heterocycl. Chem.* 11, 123 (1970).

²⁷⁵ B. R. Penfold, *Acta Cryst.* 6, 591 (1953).

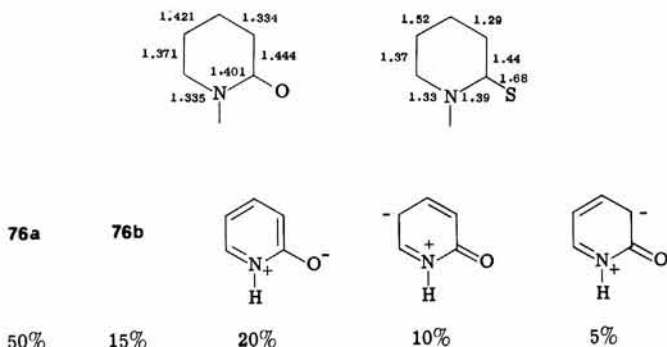


FIG. 2. Bond lengths of 2-pyridone and 2-pyridithione, and resonance structures of 2-pyridone.²⁷⁵

crystallographic data for 2-pyridone and has concluded that the bond lengths he obtained (Fig. 2) are best explained in terms of contributions from the five resonance structures indicated. The calculated percentage contributions which gave the best correspondence with the observed bond length data are indicated beneath the different forms.

The same author²⁷⁶ subsequently examined 2-pyridithione and he concluded from the dimensions obtained (Fig. 2) that the relative weighting of the contributing resonance structures are the same in both 2-pyridithione and 2-pyridone. The C-S bond was said to show about $65 \pm 5\%$ double-bond character.

A large contribution from the zwitterionic form of 4-pyridone has recently been disputed by Batts and Spinner²⁷⁷ following an examination of the system by infrared and Raman spectroscopy. These authors comment further that dipole moment data suggest that the upper limit for this contribution is of the order of 10–15%.

There appear to be no ERE data for pyridones and related compounds, and although Dewar and co-workers¹⁶ have calculated the heats of atomization for a number of structures of this type, the results were used for a discussion of tautomeric equilibria rather than for deriving values for the Dewar resonance energies. Empirical studies on tautomeric equilibria have, however, been used to estimate the difference in ERE of pyridones and pyridine (Section II,A, 4). Beak *et al.*⁴¹ studied the gas-phase 1-methyl-2-pyridone \rightleftharpoons 2-methoxypyridine equilibrium and compared the result with the equilibrium constant for the *N*-methylvalerolactam \rightleftharpoons

²⁷⁶ B. R. Penfold, *Acta Cryst.* **6**, 707 (1953).

²⁷⁷ B. D. Batts and E. Spinner, *Aust. J. Chem.* **22**, 2581 (1969).

O-methylvalerolactim equilibrium, from which they concluded that the 2-pyridone ring is 6 kcal mole⁻¹ less aromatic than that of pyridine. The present authors⁴³ have made similar comparisons for the corresponding prototropic equilibrium in the aqueous phase. These results are less rigorous but the method is more generally applicable and has been extended to 4-pyridone, 2-quinolone, and 1-isoquinolone and the related thiones, imines, and methides.⁴⁴ The results are summarized in Table IV and demonstrate that pyridones, quinolone, isoquinolone, and their related thiones and imines retain much of the resonance energy of the pyridine, quinoline, and isoquinoline structures, respectively. The methides, in which the zwitterionic canonical forms have the negative charge on a carbon atom, are substantially less aromatic.

Several discussions of aromaticity and its relationship to NMR parameters have included reference to 2- and 4-pyridones. Indeed Elvidge and Jackman⁸⁶ first applied the ring current criterion as a quantitative measure of aromaticity to 1-methyl-2-pyridone and estimated the aromaticity to be 35% that of benzene from a consideration of the chemical shifts of C-methyl substituents and of ring protons. They also concluded that the 2-methide analog was nonaromatic. Bell, Egan, and Bauer,²⁷⁸ from a consideration of the small long-range methyl to ring proton coupling constants in substituted 2-pyridones, as well as in 2-pyridithiones, concluded that considerable aromatic character must be associated with these compounds. By contrast, a Japanese group²⁷⁹ suggested that the 2-pyridone structure has a relatively localized π -system on the basis of the correlation of the methyl substituent effect on the chemical shift of *ortho* protons with π -bond orders. Dauben *et al.*⁸⁴ report a diamagnetic susceptibility for *N*-ethylpyridone of 7×10^{-6} cm³ mole⁻¹, a little over half that of benzene (Table VI).

Of the 4-pyridone series, Jackman *et al.*²⁸⁰ have reported that 1-methyl-4-pyridone sustains a weaker ring current than 1-methyl-2-pyridone, and Batts and Spinner²⁸¹ in a discussion of chemical shifts state that the "fractional aromaticity is probably not appreciable for either (4-pyridone or 4-pyridone imine)."

The different long-range coupling of a methyl group to the *ortho* hydrogen in 4-methyl-2-quinolone ($J = 1.3$ Hz) and in 4-methyl-2-chloroquinoline ($J = 1.0$ Hz) may be attributed to a lower aromaticity of the former relative to the latter.²⁷⁹

In conclusion, it can be said that the tautomeric equilibrium studies

²⁷⁸ C. L. Bell, R. S. Egan, and L. Bauer, *J. Heterocycl. Chem.* **2**, 420 (1966).

²⁷⁹ M. Ohtsuru, K. Tori, and H. Watanabe, *Chem. Pharm. Bull.* **15**, 1015 (1967).

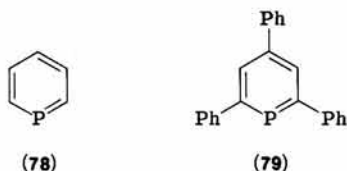
²⁸⁰ G. G. Hall, A. Hardisson, and L. M. Jackman, *Tetrahedron Suppl.* **2**, 101 (1963).

²⁸¹ B. D. Batts and E. Spinner, *Aust. J. Chem.* **22**, 2595 (1969).

give a clear indication that 2- and 4-pyridones, 2-quinolone and 1-isquinolone, and the thiones and the corresponding imino compounds have substantial aromatic character. It is unfortunate that no other ERE data are available to substantiate the results of this approach, which imply a greater aromaticity for 2-pyridone than the 35% aromatic character calculated from the controversial chemical shift data. The interpretations drawn from the remaining NMR data are of a qualitative and somewhat subjective nature.

4. Phosphabenzene and Related Compounds

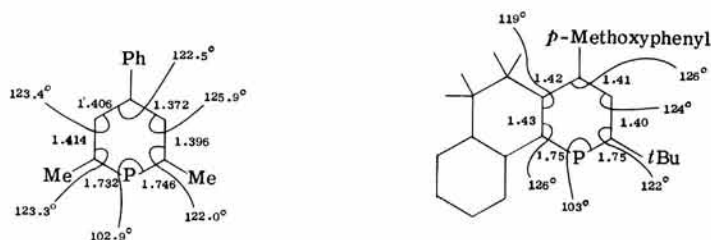
The chemistry of phosphabenzene (phosphonin) (**78**) extends back to 1966 when Märkl⁶⁵ prepared the derivative, 2,4,6-triphenylphosphabenzene (**79**), although the same author²⁸² had earlier prepared some derivatives with a pentavalent phosphorus atom, *viz.* 1,1-disubstituted phosphabenzenes. The PMR spectrum of **79** shows that all the protons absorb in the region δ 7.0–8.1 and the ³¹P signal appears at –178.2 ppm, which was said to be at unexpectedly low field. The UV spectrum exhibited a large bathochromic shift relative to both the absorptions of 1,3,5-triphenylbenzene and 2,4,6-triphenylpyridine.



Subsequently, a variety of substituted phosphabenzenes were prepared by Märkl and others (for a list of references of compounds not mentioned here, see Ashe²⁸³), recently culminating in an elegant one-step preparation of the parent compound **78** by Ashe.²⁸³ The UV absorptions of **78** are again at longer wavelength than those observed for the nitrogen analog. The most interesting physicochemical feature, however, is the PMR spectrum, which shows that the α -proton is strongly deshielded, δ 9.3, and is strongly coupled to both ³¹P ($J = 38$) and to the β -proton ($J_{23} = 10$ Hz; cf. 5.5 Hz for pyridine). The temptation is to conclude that the double-bond character is greater in phosphabenzene, but this is not supported by consideration of the chemical shifts of the β - and γ -protons, both of which appear to absorb at somewhat lower field than the corresponding protons

²⁸² G. Märkl, *Angew. Chem. Int. Ed. Engl.* **2**, 153, 479 (1963).

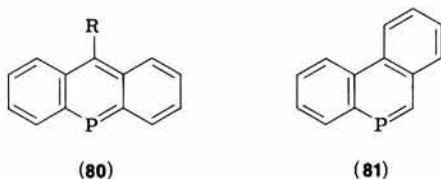
²⁸³ A. J. Ashe, *J. Amer. Chem. Soc.* **93**, 3293 (1971).

FIG. 3. Bond lengths and bond angles of phosphabenzene.^{284,285}

in pyridine. Ashe suggests that this is most consistent with an appreciable ring current in **78**.

The planarity of the phosphabenzene nucleus has been demonstrated by X-ray analyses of 2,6-dimethyl-4-phenylphosphabenzene²⁸⁴ and of a 2-butyl-4-aryl-5,6-dihydronaphtho[1,2-*b*]phosphonin.²⁸⁵ The bond lengths, which clearly imply aromatic character, and bond angles are summarized in Fig. 3.

Studies on benzo-fused analogs of **78** have also been reported. Solutions of unstable dibenzo[*b,e*]phosphabenzene (phosphaanthracene) (**80**, R = H)²⁸⁶ and dibenzo[*b,d*]phosphabenzene (phosphaphenanthrene) (**81**)²⁸⁷ have been prepared and examined by UV spectroscopy. The overall shape of the spectrum due to **80** (R = H) resembles that of anthracene rather than acridine, whereas that of **81** resembles the phenanthridine more closely than the phenanthrene spectrum. The absorptions of both **80** (R = H) and **81** show the typical strong bathochromic shifts relative to their nitrogen and carbocyclic analogs. 10-Phenyldibenzo[*b,e*]phosphabenzene (**80**, R = Ph)²⁸⁸ is more stable than its parent and shows similar UV absorption.



²⁸⁴ J. C. T. Bart and J. J. Daly, *Angew. Chem. Int. Ed. Engl.* **7**, 811 (1968).

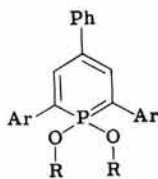
²⁸⁵ W. Fischer, E. Hellner, A. Chatzidakis, and K. Dimroth, *Tetrahedron Lett.*, **6227** (1968).

²⁸⁶ P. de Koe and F. Bickelhaupt, *Angew. Chem. Int. Ed. Engl.* **6**, 567 (1967).

²⁸⁷ P. de Koe, R. van Veen, and F. Bickelhaupt, *Angew. Chem. Int. Ed. Engl.* **7**, 465 (1968).

²⁸⁸ P. de Koe and F. Bickelhaupt, *Angew. Chem. Int. Ed. Engl.* **7**, 889 (1968).

Compounds related to phosphabenzene are those in which the phosphorus atom carries two substituents, and "aromatic bonding states" have been postulated for these in discussions of 1-alkyl-1,2,4,6-tetraphenylphosphabenzene²⁸⁹ and some 1,1-dialkoxy- and 1,1-diaryloxyphosphabenzene²⁹⁰ (82).²⁹⁰ Aromatic character of the heterocyclic ring in 82 ($R = \text{Me}$; $\text{Ar} = \text{Ph}$) can be deduced from the bond lengths of the C-C bonds, which all lie in the region 1.39–1.42 Å.²⁹¹ However, the ring deviates slightly but significantly from planarity.



(82)

The bonding about the phosphorus atom in these compounds, as well as in the simple phosphabenzene ring, has been the subject of calculations based upon two different models, one using one $d\pi$ atomic orbital and the other using two $d\pi$ atomic orbitals²⁹²; the latter model provided the better correlation with UV absorption data.

5. Arsabenzene, Stibabenzene, and Derivatives

Ashe has recently synthesized both arsabenzene (arsenin) (83)²⁸³ and stibabenzene (antimonin) (84).⁶⁶ The former is very air-sensitive while the latter polymerizes even at -80° . The NMR spectra of these, like that of phosphabenzene,²⁸³ show that the α -proton is highly deshielded and Ashe reports the following order of chemical shifts: pyridine δ 8.1, phosphabenzene δ 8.6, arsabenzene δ 9.3, and stibabenzene δ 10.7. Significantly, the more remote β - and γ -protons in each compound in the series are each at approximately the same chemical shift, which may imply an appreciable ring current for each compound. $J_{23} = 11$ Hz for both 83 and 84, which is greater than the 10 Hz found for phosphabenzene and 5.5 Hz for pyridine.

²⁸⁹ G. Märkl and A. Merz, *Tetrahedron Lett.*, 3611 (1968).

²⁹⁰ K. Dimroth and W. Städe, *Angew. Chem. Int. Ed. Engl.* 7, 881 (1968).

²⁹¹ U. Thewalt, *Angew. Chem. Int. Ed. Engl.* 8, 769 (1969).

²⁹² M. Mracec and Z. Simon, *Rev. Roum. Chim.* 16, 449 (1971).



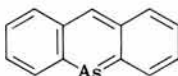
(83)



(84)

In the UV spectra, **83** shows bands at 219 and 268 $m\mu$ while **84** shows absorptions at 236 and 312 $m\mu$ (*cf.* phosphabenzene λ_{\max} 213 and 246 $m\mu$). Ashe⁶⁶ suggests that if the bands are due to $\pi \rightarrow \pi^*$ transitions, then the shifts to longer wavelengths exhibited by the heteroaromatics with the heavier atoms may arise from weaker bonding in these compounds.

Prior to Ashe's contribution to this field, dibenzo[*b,e*]arsabenzene (9-arsaanthracene) (**85**) was obtained in solution by two groups.^{293,294} The UV spectrum was shown to be very similar in overall pattern to that of 9-phosphaanthracene and of anthracene, and showed, once more, a bathochromic shift relative to each. During the final preparation of this chapter an X-ray structural determination of 2,3,6-triphenylarsabenzene was reported which shows that the geometry is consistent with a delocalized six π -electron system.²⁹⁵



(85)

6. Pyrylium Salts, Pyrones, and Related Compounds

There are two classes of potential six- π -electron systems to be discussed in this section: (a) pyrylium salts (**86**) and (b) pyrones and related compounds.

There appear to be rather few data available for the pyrylium cation. Balaban and Simon¹⁵⁹ have reported a high value of +97 for the aromaticity constant, a reflection of its electrophilicity. The PMR spectrum, as expected, shows absorptions in the 8.5–9.6 ppm region,²⁹⁶ and qualitative agreement between chemical shifts and π -electron density, as calculated by the HMO method, has been reported.²⁹⁷ Further calculations of charge

²⁹³ P. Jutzi and K. Deuchert, *Angew. Chem. Int. Ed. Engl.* **8**, 991 (1969).

²⁹⁴ H. Vermeer and F. Bickelhaupt, *Angew. Chem. Int. Ed. Engl.* **8**, 992 (1969).

²⁹⁵ F. Sanz and J. J. Daly, *Angew. Chem. Int. Ed. Engl.* **11**, 630 (1972).

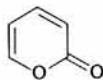
²⁹⁶ A. T. Balaban, G. R. Bedford, and A. R. Katritzky, *J. Chem. Soc.*, 1946 (1964).

²⁹⁷ C. C. Rentia, A. T. Balaban, and Z. Simon, *Rev. Roum. Chem.* **11**, 1193 (1966).

density for **86** and benzopyrylium systems have been performed using the CNDO/2 method.²⁹⁸



(86)

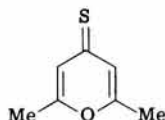


(87)

As with the pyridones (Section III,D, 3), the question of the aromaticity of 2- and 4-pyrone, **87** and **88**, is allied to that of the extent of zwitterionic character. The dipole moment, 3.7 D,²⁹⁹ of **88** suggests that contributions from dipolar forms are significant, at least for this compound. There appears to be no determination of the precise geometry of either pyrone isomer, although data are available for 2,6-dimethyl-4-pyranthione (**89**).³⁰⁰ Bond lengths of the O-C-2, C-2-C-3, and C-3-C-4 bonds are 1.37, 1.35, and 1.41 Å, respectively, from which it has been estimated that the contribution from the dipolar structure is 32%.



(88)



(89)

The ERE of 7-methylpyrano[4, 3-*b*]pyran-2,5-dione (**90**) has been determined¹⁰⁶ to be extraordinarily high at 100 kcal mole⁻¹, which suggests that the simple 2-pyrone is also strongly aromatic. Calculations of DE for both **87** and **88** have been performed by various groups. An early paper by Brown³⁰¹ reported HMO data that predict that 4-pyrone has considerable dipolar character, and subsequently Zahradník *et al.*³⁰² calculated the DE for 4-pyrone to be 2.868β and for 2-pyrone, 2.896β. Comparison of the absolute values is inappropriate in that somewhat different parameters were used for each. Beak²⁸ has further demonstrated that for HMO calculations the relative order of DE for the two rings is dependent upon the parameters chosen. More recently Hérault and Gayoso⁵⁴ have presented results of calculations for each compound,

²⁹⁸ O. Mårtensson and C. H. Warren, *Acta Chem. Scand.* **24**, 2745 (1970).

²⁹⁹ M. Rolla, M. Sanesi, and G. Traverso, *Ann. Chim. (Rome)* **42**, 673 (1952).

³⁰⁰ J. Toussaint, *Bull. Soc. Chim. Belg.* **65**, 213 (1956).

³⁰¹ R. D. Brown, *J. Chem. Soc.*, 2670 (1951).

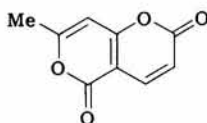
³⁰² R. Zahradník, C. Párkányi, and J. Koutecký, *Collect. Czech. Chem. Commun.* **27**, 1242 (1962).

TABLE XII
CALCULATED DATA FOR PYRONES^a

	DE (Section II, A, C)	DE _{sp} (Section II, A, C)	A ₁ (Section II, B)
2-Pyrone	1.595β (1.732)	0.199β (0.218)	0.79 (0.96)
4-Pyrone	1.598β (1.618)	0.200β (0.217)	0.72 (0.94)

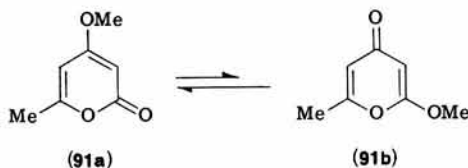
^a Values calculated by $\omega\beta$ iterative method—values in parentheses obtained from the Wheland–Pauling method.

employing both the Wheland–Pauling (WP) method and an iterative technique ($\omega\beta$). The latter gives the better agreement between the calculated and experimental dipole moments for **88**. The authors' values for DE, and DE_{sp} as well as the Julg and Francois's A₁ values (Section II,B) determined from the calculated bond lengths, are given in Table XII. Both sets of calculations suggest that the aromaticities of the two ring systems are comparable.



(90)

Experimental determinations of the relative aromaticities have not been uniformly instructive. Prior to the calculations by the French group, Beak²⁸ had surveyed various conclusions drawn from IR spectral data and basicity data and considered that much of the work was equivocal. From equilibration data on **91** he concluded that **91a** is the thermodynamically more stable.

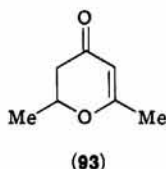
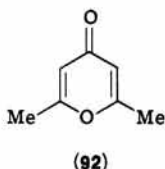


(91a)

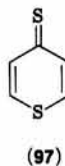
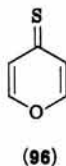
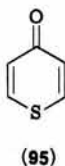
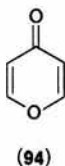
(91b)

PMR chemical shift data have been used to estimate the aromaticity of 2,6-dimethyl-4-pyrone (**92**) relative to benzene.⁹⁴ Use was made of

2,3-dihydro-2,6-dimethyl-4-pyrone (**93**) as a model and the ring current was determined to be about the same as that of benzene. By contrast the same authors pointed out that the magnetic susceptibility ($\Delta\chi \times 10^6$) of **92** is 2.19, which is small compared with values for benzene (18.7), tropolone (15.2), and furan (14.3). It is also very close to the value of 2.25 reported for **93**. Recent considerations of the molecular susceptibility anisotropies of both 2- and 4-pyrone led to the conclusion that both are nonaromatic.⁸¹



At this point it is appropriate to consider the spectral data for some pyrones and their dihydro analogs, and both chemical shift and coupling constant data are collected in Fig. 4.³⁰³⁻³⁰⁶ It is apparent that the coupling constants between *vic* protons bonded to sp^2 carbon atoms are approximately the same in both the aromatic and nonaromatic models. A further comparison of data for **94** to **97** provided by Jonas *et al.*,¹²⁰ some of which has been independently duplicated by Brown and Bladon,³⁰⁷ provides an example of a case in which a simple comparison of the orders of chemical shifts and of coupling constants give different orders of aromaticity within the series.



It is evident that, for pyrones, the available data are contradictory. The enormous ERE of **90** and the estimate of the ring current in **92**, which is

³⁰³ W. H. Pirkle and M. Dines, *J. Heterocycl. Chem.* **6**, 1 (1969) and references therein.

³⁰⁴ S. S. Dharmatti, G. Govil, C. R. Kanekar, C. L. Khetrepal, and Y. P. Virmani, *Proc. Indian Acad. Sci. Sect. A* **56**, 71 (1962); *Chem. Abstr.* **58**, 3027f (1963).

³⁰⁵ (a) T. J. Batterham and J. A. Lamberton, *Aust. J. Chem.* **17**, 1305 (1964); (b) A. K. Kiarg and S. F. Tan, *J. Chem. Soc.*, 2283 (1965); (c) M. M. Badawi and M. B. E. Fayez, *Indian J. Chem.*, **5**, 93 (1967).

³⁰⁶ E. M. Kosower and T. S. Sorensen, *J. Org. Chem.* **28**, 687 (1963).

³⁰⁷ N. M. D. Brown and P. Bladon, *Spectrochim. Acta* **21**, 1277 (1965).

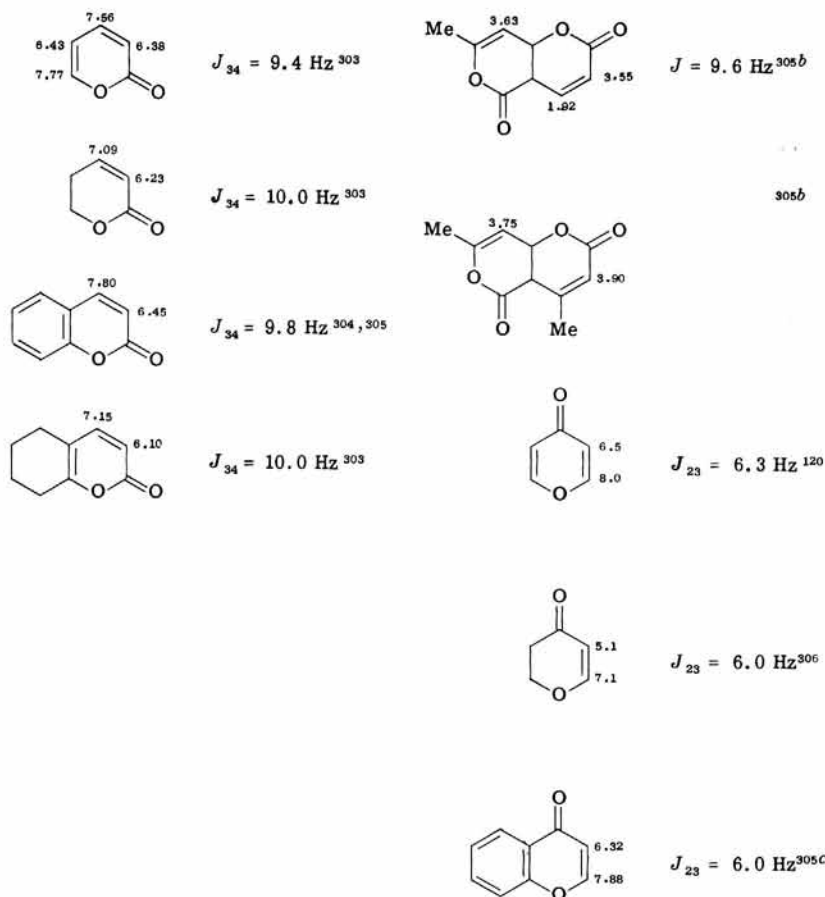


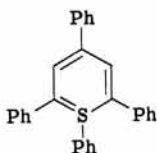
FIG. 4. PMR spectral data for pyrones (in ppm). Data obtained in CDCl_3 except that reported by Kosower and Sorensen.³⁰⁶

substantially greater than the estimate of the ring current in 2-pyridone, are disconcerting, as is the disparity between the conclusions to be drawn from the ring current and magnetic susceptibility data for **92**. The validity of the ERE value and the ring current estimate certainly seem suspect.

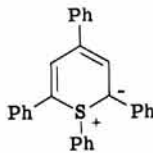
7. Thiabenzene, Thiapyrylium, Thiapyrones, and Related Compounds

As well as the sulfur analogs of pyrylium cation and the pyrones (to be considered later in this section), a third important series of six-membered sulfur heteroaromatic is known: the thiabenzenes.

The first example of this last class (**98**), where "tetravalent bonding" occurs through valence-shell expansion (for a review of this topic see Salmond³⁰⁸), was obtained in 1961³⁰⁹ and there are still rather few examples known. Discussion has centered upon the nature of the participation by the 3d orbitals and whether the compounds may be regarded as being aromatic or of the ylide type.

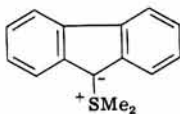


(98a)

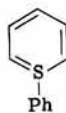


(98b)

The low dipole moments of **98** (1.88 D) and of various benzofused analogs, compared with the dipole moment of 6.2 D for **99**, have been cited by Price *et al.*³¹⁰ as evidence that the covalent structure is a more reasonable representation than the ylide, e.g., **98b**. The further preparation of **100** by the same group³¹¹ has recently been described and here the NMR



(99)



(100)

spectrum shows a multiplet at 7.2 ppm. The dipole moment, 0.8 D, is significantly less than that of **98**, and the lack of steric hindrance here, the authors suggest, allows the two rings to become coaxial, with a resultant decrease in ylide-type character. In the coaxial structure π -overlap with a 3p orbital is envisaged, while in the bent form overlap with the single 3d_{zz} orbital is proposed. Both models in fact allow a cyclic aromatic ring current.³¹² By contrast, Hortmann and Harris³¹³ report that **101** shows substantial ylide-type character (in particular, H-2, 6 are shielded in the

³⁰⁸ W. G. Salmond, *Quart. Rev.* **22**, 253 (1968).

³⁰⁹ G. Suld and C. C. Price, *J. Amer. Chem. Soc.* **83**, 1770 (1961).

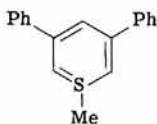
³¹⁰ C. C. Price, M. Hori, T. Parasaran, and M. Polk, *J. Amer. Chem. Soc.* **85**, 2278 (1963).

³¹¹ M. Polk, M. Siskin, and C. C. Price, *J. Amer. Chem. Soc.* **91**, 1206 (1969).

³¹² C. C. Price, J. Follweiler, H. Pirelahi, and M. Siskin, *J. Org. Chem.* **36**, 791 (1971).

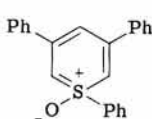
³¹³ A. G. Hortmann and R. L. Harris, *J. Amer. Chem. Soc.* **92**, 1803 (1970).

PMR spectrum), and they suggest^{313,314} that the lack of evidence for a ring current lends support to the bonding scheme discussed by Dewar³¹⁵ wherein two $3d$ orbitals are involved in weak overlap with the π -system.

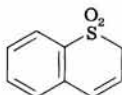


(101)

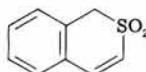
Thiabenzene 1-oxides (e.g., **102**) have also figured in the above discussion. Earlier papers³¹⁶⁻³¹⁸ did not rule out the possibility of aromatic conjugation in these compounds, but NMR data are suggestive of ylide character, and bonding of the ylide type has recently been firmly proposed by Hortmann and Harris.^{313,314} Somewhat related systems are the anions derived from cyclic sulfones such as **103** and **104**. Pagani *et al.*³¹⁹⁻³²¹ have



(102)



(103)



(104)

suggested, from NMR evidence, that the negative charge on the anions is delocalized, and from the kinetic acidities of the precursors and stabilities of the anions have surmised that these anions are aromatic in character.³²⁰ By contrast³²² a lack of aromaticity was earlier deduced for **105**, and, from an X-ray study, diene character has been suggested for the π -isoelectronic structure **106**³²³

³¹⁴ A. G. Hortmann and R. L. Harris, *J. Amer. Chem. Soc.* **93**, 2471 (1971).

³¹⁵ M. J. S. Dewar, "The Molecular Orbital Theory in Organic Chemistry," pp. 430-436. McGraw Hill, New York, 1969.

³¹⁶ A. G. Hortmann, *J. Amer. Chem. Soc.* **87**, 4972 (1965).

³¹⁷ Y. Kishida and J. Ide, *Chem. Pharm. Bull. Jap.* **15**, 360 (1967).

³¹⁸ B. Holt, J. Howard, and P. A. Lowe, *Tetrahedron Lett.*, 4927 (1969).

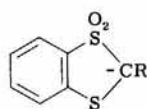
³¹⁹ S. Bradamante, A. Mangia, and G. Pagani, *Tetrahedron Lett.*, 3381 (1970).

³²⁰ S. Bradamante, S. Maiorana, A. Mangia, and G. Pagani, *J. Chem. Soc. B*, 74 (1971).

³²¹ S. Bradamante, A. Mangia, and G. Pagani, *J. Chem. Soc. B*, 545 (1971).

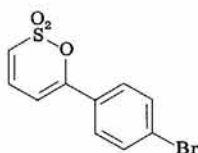
³²² R. Breslow and E. Mohacsi, *J. Amer. Chem. Soc.* **84**, 684 (1962).

³²³ W. E. Barnett, M. G. Newton, and J. A. McCormack, *J. Chem. Soc. Chem. Commun.*, 264 (1972).



R = H or CO₂Et

(105)

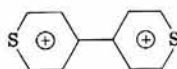


(106)

The thiapyrylium cation **107** is generally regarded as being an aromatic structure. An early calculation³⁰ predicted high stability for the ring, and proton signals in the NMR spectrum show the expected downfield shifts (δ 9–10.4).³²⁴ The NMR spectra of a large number of polynuclear thiapyrylium cations have been reported³²⁵ and attempts were made to correlate chemical shifts with electron density, which proved somewhat difficult due to deshielding effects of neighboring rings. Recently the novel dithiopyrylium dication **108** has been prepared,³²⁶ and the NMR spectrum shows a further downfield shift of 0.2–0.25 ppm relative to **107**.



(107)



(108)

The thiapyrones have received rather less attention than their oxygen analogs. The values of the heats of combustion of 2,6-diphenyl-4-thiapyrone and of 2,6-diphenyl-4*H*-thiapyran were used to estimate the resonance energy of 4-thiapyrone to be 33 kcal mole⁻¹,³²⁷ which can be taken as clear evidence of substantial aromatic character. Zahradník and co-workers²⁹ calculated the DE of approximately 1.6 β for 4-thiapyrone and 1.5 β for 2-thiapyrone, and both 2- and 4-thiothiapyrones. The mean chemical shift of the α - and β -protons in both 4-thiapyrone (**95**) and 4-thiothiapyrone (**97**) are downfield relative to the values for the same parameter in 4-pyrone and 4-thiapyrone and this has been interpreted in terms of a larger ring current in the sulfur heterocycles.¹²⁰

8. Borabenzene Anion

The borabenzene anion is a potential six- π -electron structure which has received attention only recently. PMR and ¹¹B-NMR data have

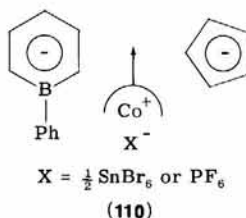
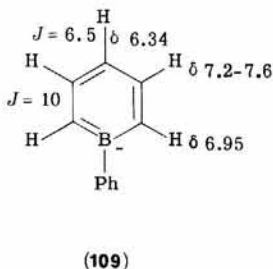
³²⁴ K. Dimroth, W. Kinzebach, and M. Soyka, *Chem. Ber.* **99**, 2351 (1966).

³²⁵ T. E. Young and C. J. Ohnmacht, *J. Org. Chem.* **32**, 1558 (1967).

³²⁶ Z. Yoshida, S. Yoneda, T. Sugimoto, and O. Kikukawa, *Tetrahedron Lett.*, 3999 (1971).

³²⁷ L. Lorenz-Oppan and H. Sternitzke, *Z. Elektrochem.* **40**, 501 (1934).

now been reported for the 1-phenylborabenzene anion **109** as a ligand in a transition metal π -complex **110**³²⁸ and also as the free ion in solution.³²⁹ PMR data shown refer to the free ion in THF-*d*₈. From the ¹¹B shifts and a comparison of the proton shifts with those of the protons in cyclopentadienyl anion it would appear that the negative charge resides to a considerable extent on the boron atom and that the system probably supports a ring current.



9. Diazines, Triazines, Tetrazines, and Related Compounds

There have been a number of quantitative estimates of the aromatic character of the azines and particular attention has been paid to the determination of their stabilities, by both empirical and theoretical approaches. Maccoll³³⁰ compiled an extensive series of data for all possible di-, tri-, tetra-, and pentazines, obtained from a valence-bond approach, while other groups^{21,267,331} have obtained less extensive results using the MO method. Heat of combustion data for the diazines have been used to determine ERE values^{332,333} and some of the calorimetric data have been used further by Cox⁷ to calculate conjugation energies (Section II,A, 1). Dewar resonance energies have been reported for a limited number of structures and include two benzo-fused analogs.^{9,13} The results of each of these approaches are summarized in Table XI (Section III,D, 1). For pyridazine, results vary depending upon the choice of an =N—N= or an —N=N— model. The values reported by Tjebbes³³² appear to be rather too low. It has been remarked that data for the diazines fail to fit a DE versus ERE correlation observed for other compounds.²⁰ Dauben

³²⁸ G. E. Herberich, G. Greiss, and H. F. Heil, *Angew. Chem. Int. Ed. Engl.* **9**, 805 (1970).

³²⁹ A. J. Ashe and P. Shu, *J. Amer. Chem. Soc.* **93**, 1804 (1971).

³³⁰ A. Maccoll, *J. Chem. Soc.*, 670 (1946).

³³¹ M. Simonetta, *J. Chim. Phys.* **49**, 68 (1952).

³³² J. Tjebbes, *Acta Chem. Scand.* **16**, 916 (1962).

³³³ A. F. Bedford, A. E. Beezer, and C. T. Mortimer, *J. Chem. Soc.*, 2039 (1963).

*et al.*³⁴ report that the diamagnetic susceptibility exaltation of pyrazine is only a little over half that of pyridine.

Berezin¹⁶² has calculated the coefficients of influence (Section II,F, 3) for four azines, including pyridine, and points out that the values decrease in the same order as the magnitude of the aromaticity constants increase (although pyridine or pyrazine appears to be anomalous).

X-Ray data for pyrimidine,³³⁴ pyrazine,³³⁵ *s*-triazine,³³⁶ and *s*-tetrazine³³⁷ demonstrate the aromatic character of the rings, but the data have not been used for a quantitative comparison of aromaticity. It has been noted that the C-N-C bond angles in each compound are less than 120° cf. pyridine, Section III,D, 1), and from a consideration of the perturbation on the ring angles on going from benzene to pyridine, Coulson and Looyenga³³⁸ have calculated the bond angles in the diazines, *s*-triazine, and *s*-tetrazine. Their results are in good agreement with the available experimental data (see also Kim and Hamerka³³⁹).

The "hydroxy derivatives" of the diazines exist predominantly in the oxo form where such tautomerism is possible, but, unlike the pyridones, the aromaticity of these compounds has excited rather little attention. In an early paper Pauling and Sherman²⁷¹ provided extensive data for the resonance energies of a large number of molecules, which included a series of ureides and purines. Inspection of the results shows that a structure such as 4-methyluracil has substantial excess resonance energy over the sum of the resonance energies for two amide groups (see also Tack²⁷³).

Bauer *et al.*³⁴⁰ examined NMR spectra of 4-pyrimidones, 4-pyrimidithiones, and 4-substituted pyrimidines, and from an assessment of coupling constant and chemical shift data drew the qualitative conclusion that the former two structures have less aromatic character than the pyrimidine ring. Pfeleiderer³⁴¹ has come to a similar conclusion using the same criteria but applied to 2- and 4-pyrimidones. He has argued further from a discussion of acidity of various uracils that the amide groups do not contribute in cyclic resonance in these ring systems.³⁴²

³³⁴ P. J. Wheatley, *Acta Crystallogr.* **13**, 80 (1960).

³³⁵ P. J. Wheatley, *Acta Crystallogr.* **10**, 182 (1957).

³³⁶ P. J. Wheatley, *Acta Crystallogr.* **8**, 224 (1955).

³³⁷ F. Bertinotti, G. Giacomello, and A. M. Liquori, *Acta Crystallogr.* **9**, 510 (1956).

³³⁸ C. A. Coulson and H. Looyenga, *J. Chem. Soc.*, 6592 (1965).

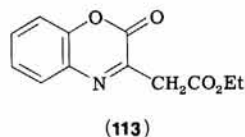
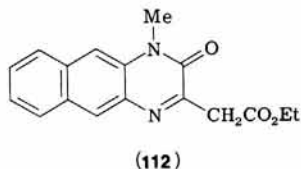
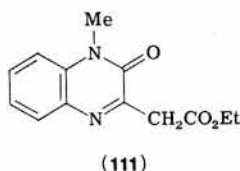
³³⁹ H. Kim and H. F. Hamerka, *J. Amer. Chem. Soc.* **85**, 1398 (1963).

³⁴⁰ L. Bauer, G. E. Wright, B. A. Mikrut, and C. L. Bell, *J. Heterocycl. Chem.* **2**, 447 (1965).

³⁴¹ W. Pfeleiderer, in "Topics in Heterocyclic Chemistry" (R. N. Castle, ed.), p. 77. Wiley (Interscience), New York, 1969.

³⁴² W. Pfeleiderer, in "Topics in Heterocyclic Chemistry" (R. N. Castle, ed.), p. 75. Wiley (Interscience), New York, 1969.

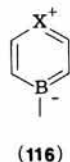
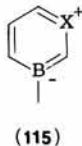
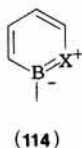
Finally, Mondelli and Merlini³⁴³ have discussed the relationship between aromatic character and the extent of enamine tautomerism in **111**, **112**, **113**, and related derivatives, but they came to no specific conclusions.



Overall, there is evidently a reduction in aromatic character on introduction of further nitrogen atoms into the ring system. Although it is difficult to assess this quantitatively for the derivatives discussed above, there is substantial evidence to support this view for the unsubstituted systems. In connection with this Pfeleiderer³⁴⁴ has stated that "the polarity of the C=N bonds increases (in di- and triazines) since more π -electrons are partially located at the heteroatoms . . . resulting in a decrease in the stabilization energy, or in other words, of the heteroaromatic character."

10. "Borazaro-" and "Boroxaro" Rings

Dewar and co-workers have provided extensive contributions to the development of the chemistry of six-membered rings containing boron plus a further heteroatom capable of donating electrons to the vacant p -orbital in boron, the resultant structures having six π -electrons. Of the three possible structurally isomeric rings **114**, **115**, and **116** (where X is an electron donor atom) the first type has received the greatest attention. The majority of work has involved rings containing nitrogen as the electron donor.

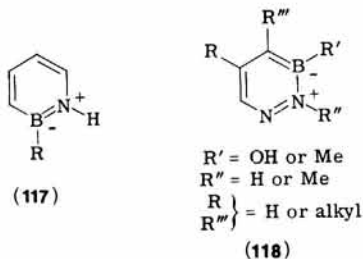


The unsubstituted borazarene (**117**, R = H), the trivial name for 2,1-borazarobenzene (for an explanation of the nomenclature see Ref. 63)

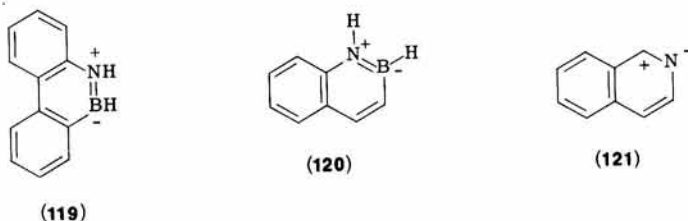
³⁴³ R. Mondelli and L. Merlini, *Tetrahedron* **22**, 3253 (1966).

³⁴⁴ W. Pfeleiderer, in "Topics in Heterocyclic Chemistry" (R. N. Castle, ed.), p. 63. Wiley (Interscience), New York, 1969.

is apparently unstable,³⁴⁵ in marked contrast to its polycyclic analogs,⁶³ and the recently reported 3,2-borazaropyridines (**118**).³⁴⁶ A phenyl substituent at the Boron atom enhances the stability of a borazarene.³⁴⁷ The aromatic character, as well as the background and synthetic pathways, have been discussed by Dewar⁶³; accordingly, only a rather brief survey will be given here.



Simple HMO calculations⁶³ on **119** and **120** suggest that contributions from dipolar structures are not very important, though "appreciable" resonance energy was implied. Low dipole moments characteristic of these structures may, however, arise not from a lack of dipolar character, but from a cancellation of σ -bond and π -bond moments operating in opposite directions.⁷¹ UV and NMR absorptions have provided a useful base for discussions of aromatic character. The UV absorptions of borazaro compounds often closely resemble the spectra of nitrogen heterocycles. Thus 10,9-borazarophenanthrene (**119**) and phenanthrene show similar absorptions⁶⁴ and the spectra of 2,1-borazaronaphthalene (**120**) and isoquinoline are nearly superimposable.⁶³ The latter similarity has been qualitatively explained by considering contributions from dipolar canonical forms (**121**) to the structure of the latter.



PMR spectra show absorptions in the aromatic region, e.g., **117**

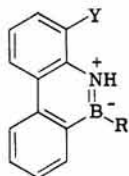
³⁴⁵ K. M. Davies, M. J. S. Dewar, and P. Rona, *J. Amer. Chem. Soc.* **89**, 6294 (1967).

³⁴⁶ J. Namtvedt and S. Gronowitz, *Acta Chem. Scand.* **22**, 1373 (1968).

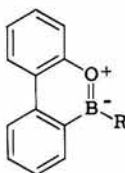
³⁴⁷ D. G. White, *J. Amer. Chem. Soc.* **85**, 3634 (1963).

(R = Ph) absorbs at δ 6.3–7.8,³⁴⁷ and similar low-field shifts have been reported by Gronowitz and Maltesson for 3,2-borazaropyridines.³⁴⁸ These authors suggested that the magnitude of ortho side chain coupling constants indicates that the C-4–C-5 bond order is higher than that of the C-5–C-6.

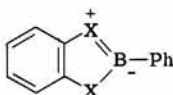
Dewar and co-workers³⁴⁹ have considered the ^{11}B -NMR shifts of various compounds and suggested that two factors affect the boron chemical shifts: π -donation to the vacant boron p -orbital, and the presence of additional lone pairs, over and above those necessary for bonding, on the adjacent atom. From a consideration of these two factors and the chemical shifts of open-chain boron compounds and both five- and six-membered ring compounds including **122**–**125**, they argued that π -bonding is more important in the cyclic series as would be anticipated if these are aromatic. They further deduced that the boroxaro compounds **123** are less aromatic than the nitrogen analogs **122**, as had been suggested earlier,⁶³ and also that an electron-withdrawing group, e.g., as in **122e** opposes π -bonding



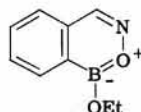
- (122a) R = Me, X = H
 (122b) R = OEt, Y = H
 (122c) R = Ph, Y = H
 (122d) R = Cl, Y = H
 (122e) R = Me, Y = NO₂



- R = OEt or Cl
 (123)

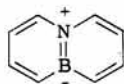


- X = NH or O
 (124)

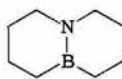


- (125)

between the nitrogen and boron atoms, so reducing the aromatic character of the system. The upfield ^{11}B shifts for 10,9-borazaronaphthalene (**126**) relative to the decalin analog **127** may again be partly accounted for by the aromaticity of the former, although the differences in the ^{11}B shifts may arise simply from the different hybridizations of the carbon atoms α to the boron atom.³⁵⁰



- (126)



- (127)

³⁴⁸ S. Gronowitz and A. Maltesson, *Acta Chem. Scand.* **25**, 2435 (1971).

³⁴⁹ F. A. Davis, M. J. S. Dewar, and R. Jones, *J. Amer. Chem. Soc.* **90**, 706 (1968).

³⁵⁰ F. A. Davis, M. J. S. Dewar, R. Jones, and S. D. Worley, *J. Amer. Chem. Soc.* **91**, 2094 (1969).

That the $\overset{-}{B} = \overset{+}{N}$ bond can take part in aromatic delocalization is amply demonstrated by the very similar physical and chemical properties of **126** and naphthalene itself.⁷¹ In particular, X-ray powder photographs of the two compounds are superimposable and the UV spectra compare favorably. The mass spectra are also similar, although **126** gives a greater yield of fragmentation products. This has been interpreted as support for the view that **126** is aromatic but somewhat less so than naphthalene itself.

11. Dithiin, Dioxin, and Derivatives

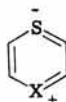
Simple considerations of six-membered rings containing two Group VI elements lead to the conclusion that the rings will not obey the $4n + 2$ rule. However some aromatic character has been attributed³⁵¹⁻³⁵³ to the 1,4-dithiin (**128**) and 1,4-oxathiin (**129**) rings and also to their benzo-fused analogs; contributions of the type **130** have been envisaged in which there is a valence expansion of the sulfur valence shell.



(128)

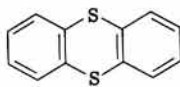


(129)



(130)

X-Ray structure determinations of 1,4-dithiin³⁵⁴ and of thianthrene (**131**)³⁵⁵ show that the heterocyclic ring is boat-shaped and this may well



(131)

accommodate *d*-orbital participation. The short C-C bond lengths of 1.29 Å and the nearly normal C-S bond lengths in **128**,³⁵⁴ however, seem to be inconsistent with extensive delocalization. Various MO calculations of differing degrees of sophistication have been performed on these structures. A large DE was calculated for both **128**³⁵⁶ and **129**³⁵³ using the LCAO-MO

³⁵¹ W. E. Parham, T. M. Roder, and W. R. Hasek, *J. Amer. Chem. Soc.* **75**, 1647 (1953).

³⁵² W. E. Parham and J. D. Jones, *J. Amer. Chem. Soc.* **76**, 1068 (1954).

³⁵³ A. K. Chandra, *Tetrahedron* **19**, 471 (1963).

³⁵⁴ P. A. Howell, R. M. Curtis, and W. N. Lipscomb, *Acta Crystallogr.* **7**, 498 (1954).

³⁵⁵ H. Lynton and E. G. Cox, *J. Chem. Soc.*, 4886 (1956).

³⁵⁶ M. M. Kreevoy, *J. Amer. Chem. Soc.* **80**, 5543 (1958).

method, neglecting overlap and *d*-orbital participation. However, in a more sophisticated treatment³⁵⁷ of **128**, though still neglecting *d*-orbitals, the DE was substantially reduced. A more recent SCF-MO calculation showed high double-bond character in **128**, **129**, and their benzo-fused analogs.³⁵⁸ The NMR spectrum of **128** shows a peak at δ 5.95 which is indicative of a vinyl thioether. The isomeric 1,2-dithiin (**132**) also absorbs in this region at δ 6.13 and 5.97.³⁵⁹



(132)

The 1,4-dioxin ring system **133** is less likely to show aromatic character than the sulfur analogs discussed above and this view has received some theoretical support.^{358,360} Early workers^{361,362} had, however, assumed that the ring was planar, and bond lengths, obtained from an electron diffraction study, which fitted a planar model were interpreted as arising from some conjugation of the type illustrated in **134**,³⁶¹ a view which received support from an examination of the UV spectrum.³⁶² Later, the vibrational spectrum and the NMR absorption at δ 5.5 showed that conjugation and aromatic ring current are both negligible,⁶⁴ and no evidence of aromatic character was detected on comparing the NMR spectra of 1,4-benzodioxin and 1,4-dioxene (**135**).¹³²



(133)



(134)



(135)

E. SEVEN-MEMBERED HETEROAROMATIC RING COMPOUNDS

Simple applications of the Hückel rule predict that borepin should be aromatic, it being isoelectronic with cycloheptatrienyl (tropylium) cation, while the unsaturated seven-membered rings containing an oxygen, nitrogen, or sulfur atom are potentially antiaromatic. Discussion of antiaromaticity is outside the scope of this review but because of the

³⁵⁷ D. S. Sappinfield and M. Kreevoy, *Tetrahedron*, (Suppl. 2), **19**, 157 (1963).

³⁵⁸ M. Kamiya, *Bull. Chem. Soc. Jap.* **43**, 3929 (1970).

³⁵⁹ W. Schroth, F. Billig, and G. Reinhold, *Angew. Chem. Int. Ed. Engl.* **6**, 698 (1967).

³⁶⁰ R. J. Wratten and M. A. Ali, *Mol. Phys.* **13**, 233 (1967).

³⁶¹ J. Y. Beach, *J. Chem. Phys.* **9**, 54 (1941).

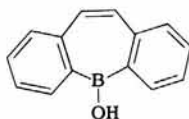
³⁶² L. W. Pickett and E. Sheffield, *J. Amer. Chem. Soc.* **68**, 216 (1946).

current interest in oxepins, azepines, and thiepins, a brief survey of these precedes discussion of compounds which are potential ten- π -electron systems in Section III,E,2.

1. Borepin Derivatives

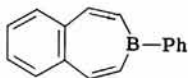
There have been very few studies on the borepin ring system and accordingly discussions of its aromatic character have been sparse. Balaban and Simon¹⁵⁹ calculated a K value (aromaticity constant) of +28, which is much lower than for tropylium cation (+100). Further evidence of aromaticity has been based very much on qualitative interpretations of spectral features.

The first borepin derivative to be prepared was the dibenzoderivative **136**³⁶³ and subsequently Dewar commented³⁶⁴ that it was unlikely to be

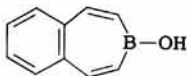


(136)

aromatic in view of the low stability associated with the isoelectronic dibenzotropylium cation. More recently the phenylbenzoborepin (**137**)¹⁰⁷ and the benzoborepinol (**138**)³⁶⁵ have been synthesized and spectroscopic evidence is consistent with some aromatic character of the seven-membered ring. The borepin protons in each are deshielded (δ 8.22 and 7.22 ppm for **137** and 8.02 and 6.68 ppm for **138**), and the UV spectra of **137** and **138** are said to resemble closely the spectra of benzotropylium and hydroxybenzotropylium (**139**), respectively. The NMR spectrum of the dithio-



(137)



(138)



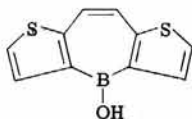
(139)

³⁶³ E. E. van Tamelen, G. Brieger, and K. G. Untch, *Tetrahedron Lett.* **8**, 14 (1960).

³⁶⁴ M. J. S. Dewar, *Progr. Boron Chem.* **1**, 236 (1964).

³⁶⁵ G. Axelrad and D. Halpern, *Chem. Commun.*, 291 (1971).

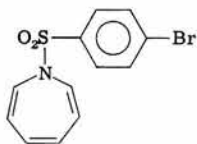
phenoborepinol (**140**), prepared recently by Gronowitz *et al.*,³⁶⁶ shows the borepin ring protons at 7.02 ppm. Too many factors are involved to allow conclusions to be drawn about the compound's aromaticity, but **140** is of interest in that it may provide a route via desulfurization to the first simple borepin ring compound.



(140)

2. Azepines, Oxepins, Thiepins, and Some Related Compounds

Recently Paquette³⁶⁷ reviewed the physical data on azepines, oxepins, and thiepins and discussed concisely the question of antiaromaticity in these systems. In short, the rings may suffer antiaromatic destabilization if they assume a planar conformation, a conformation which may also be destabilized by ring strain. X-Ray data for **141**³⁶⁸ and kinetic data derived from variable-temperature NMR studies on benzene oxide \rightleftharpoons oxepin (**142**)³⁶⁹ equilibria suggest that these rings exist in boat conformations (**143**). Recent X-ray analysis has revealed that the related diazepine (**144**) also exists in a boat conformation in the solid state.³⁷⁰



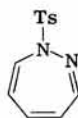
(141)



(142)



(143)



(144)

Since the publication of Paquette's review, Dewar *et al.* have performed SCF-MO calculations on a range of known and as yet unknown azepine, oxepin,¹¹ and thiepin¹⁰ structures. Calculations predict that oxepin (**142**)

³⁶⁶ S. Gronowitz, P. Gassne, and B. Yom-Tov, *Acta Chem. Scand.* **23**, 2927 (1969).

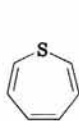
³⁶⁷ L. A. Paquette, in "Nonbenzenoid Aromatics," (J. P. Snyder, ed.), Vol. I, p. 249. Academic Press, New York, 1969.

³⁶⁸ I. C. Paul, S. M. Johnson, L. A. Paquette, J. H. Barrett, and R. J. Haluska, *J. Amer. Chem. Soc.* **90**, 5023 (1958).

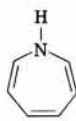
³⁶⁹ H. Günther, *Tetrahedron Lett.*, 4085 (1965).

³⁷⁰ R. Allmann, A. Frankowski, and J. Streith, *Tetrahedron* **28**, 581 (1972).

has a slightly positive Dewar resonance energy of $0.12 \text{ kcal mole}^{-1}$, whereas the unknown thiepin (**145**) and azepine (**146**) have small negative reson-

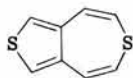


(145)

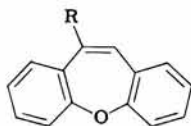


(146)

ance energies of -1.45 and $-1.8 \text{ kcal mole}^{-1}$, respectively. Calculations on mono-, di-, and tribenzo-fused structures predict that where fusion is to a carbon-carbon double bond of the seven-membered ring, then values of the resonance energy are very similar to that calculated for the corresponding number of free benzene rings (see Table III). Where fusion destroys the benzene conjugation the resonance energy is very low. The thiophene derivative **147** was predicted to have a lower resonance energy than thiophene—a result which is discussed in the light of other data for this compound in Section III, H, 1. Calculated bond lengths in all the above compounds are similar to those expected for polyene structures; earlier an LCAO calculation³⁷¹ had predicted a greater bond order for the 10, 11 bond in **148** ($R = H$) over the corresponding bond in phenanthrene.



(147)



(148)

Proton chemical shift data for various derivatives of azepines,^{367, 372} oxepins,³⁶⁷ and thiepins³⁷³ suggest that the systems are best regarded as polyenes. The oxepin **148** ($R = \text{Me}$) shows a larger coupling between the C-10 methyl group and the C-11 proton than the comparable coupling in 9-methylphenanthrene, which could be indicative that the double-bond character of the ring C-C bond is greater in the former, but which could also be explained in terms of a ring size effect.

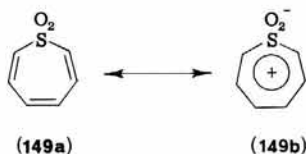
By contrast with the above ring systems, thiepin-1,1-dioxide (**149**) is a structure which has been regarded as being capable of supporting a

³⁷¹ P. M. G. Bavin, K. D. Bartle, and D. W. Jones, *J. Heterocycl. Chem.* **5**, 327 (1968).

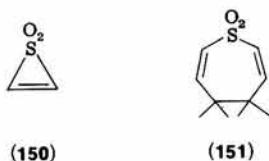
³⁷² R. J. Sundberg and R. H. Smith, *Tetrahedron Lett.*, 267 (1971).

³⁷³ H. Hofmann and H. Westernacher, *Angew. Chem. Int. Ed. Engl.* **5**, 958 (1966).

six- π -electron structure by invoking electron withdrawal onto the oxygen and/or possible participation of the vacant d -orbitals (**149b**); if analogies



are sought, then **149** is the "six- π -electron" analog of **150** which was considered in Section III,A. Mock³⁷⁴ successfully synthesized **149** in 1967 but found that the UV absorption was similar to that of cycloheptatriene and that the PMR spectrum showed absorptions at δ 6.5–7.2, which is reminiscent of a polyene. An X-ray crystallographic determination³⁷⁵ of the structure showed that the molecule exists in a shallow boat conformation. The carbon-carbon bond lengths show high bond alternation, indicative of polyene character, but the C-S bonds are unusually short, which suggested some specific conjugation between sulfur and the C-1 and C-6 atoms. A more refined analysis of the NMR spectrum has recently been published³⁷⁶ and the coupling constants are considered to be consistent with the flattened boat structure which is adopted in the solid state. Comparison of the chemical shifts with those in cycloheptatriene and the dihydro ring (**151**) suggested that thiepin 1,1-dioxide has some extra π -electron delocalization over and above the simple valence-bond structure (**149a**), but clearly the ring can hardly be classified as aromatic.



If further heteroatoms carrying lone pairs of electrons are introduced into a ring then it is conceivable that a seven-membered ring can become aromatic by virtue of its being a ten- π -electron system. Of the two arrangements of heteroatoms, **152** and **153**, the former is the more feasible for

³⁷⁴ W. L. Mock, *J. Amer. Chem. Soc.* **89**, 1281 (1967).

³⁷⁵ H. L. Ammon, P. H. Watts, J. M. Stewart, and W. L. Mock, *J. Amer. Chem. Soc.* **90**, 4501 (1968); H. L. Ammon, P. H. Watts, and J. M. Stewart, *Acta Crystallogr., Sect. B* **26**, 1079 (1970).

³⁷⁶ M. P. Williamson, W. L. Mock, and S. M. Castellano, *J. Magn. Res.* **2**, 50 (1970).



X, Y, or Z = S, O,
or NR

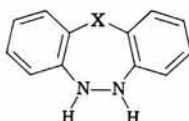
(152)



X, Y, or Z = S, O,
or NR

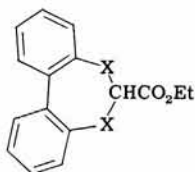
(153)

study. Vol'pin,³⁷⁷ however, has commented that a structure such as **152** with two adjacent nitrogen atoms has an insufficient number of molecular orbitals to contain all the p -electrons (see also Section III,F, 1). Allinger and Youngdale³⁷⁸ examined a series of the dibenzo-fused analogs (**154a-e**) and found that the UV spectra in all were rather similar, suggesting a lack of delocalization in the ten- π -electron system. The sulfur analog **154e**, however, is a slightly weaker base than the carbon analog **154a** (pK_a 's 2.81 and 3.10), which implies a small degree of aromatic character in the former, and indeed an NMR study showed that the hydrazo protons of **154e** were somewhat deshielded with respect to those in **154a**. The authors concluded that while **154a-d** are nonaromatic, **154e** may have some aromatic character.

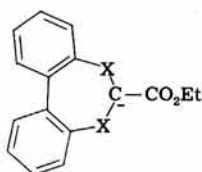


(154a) X = CH₂
(154b) X = NH
(154c) X = NMe
(154d) X = O
(154e) X = S

Breslow and Mohacsi³⁷⁹ reported acidity studies on **155a**, **155b**, and their open-chain analogs, but the similar acidities of the cyclic compounds and



(155a) X = S
(155b) X = O



(156a) X = S
(156b) X = O

³⁷⁷ M. E. Vol'pin, *Russ. Chem. Rev.* **29**, 129 (1960).

³⁷⁸ N. L. Allinger and G. A. Youngdale, *J. Amer. Chem. Soc.* **84**, 1020 (1962).

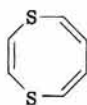
³⁷⁹ R. Breslow and E. Mohacsi, *J. Amer. Chem. Soc.* **85**, 431 (1963).

their noncyclic counterparts argued against aromatic character in the anions **156a** and **156b**. The authors suggested that strain factors may have hindered the rings becoming planar.

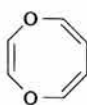
F. EIGHT-MEMBERED HETEROAROMATIC RING COMPOUNDS

1. Neutral Compounds

From the results of MO calculations, Balaban and Simon³⁸⁰ predicted that the resonance energy of the planar conformation of **157** might be sufficient to overcome strain energy involved in achieving planarity; by contrast the oxygen analog **158** was predicted to be nonplanar and hence

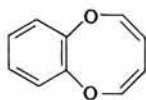


(157)



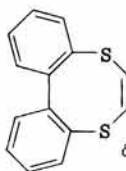
(158)

nonaromatic. Schroth and co-workers prepared the first derivatives of these—the benzo-fused compounds **159**³⁸¹ and **160**³⁸²—and more recently



δ 6.95, 5.35

(159)



δ 6.26

(160)

other groups have studied **161**³⁸³ and the nitrogen analog **162**.³⁸⁴ The chemical shifts of the protons on the eight-membered rings are shown on the diagrams and the values are inconsistent with the presence of an appreciable ring current in these compounds. The UV spectra, where reported, show a lack of conjugation, indicative that the molecules exist in tub-shaped conformations. However, in sharp contrast, Riley and Park³⁸⁵ prepared and examined the first non-benzo-fused analog **163**, and here the authors suggested that the F NMR shifts indicate the existence of a ring current. If this is indeed the case, then Balaban and Simon's prediction is well fulfilled.

³⁸⁰ A. T. Balaban and Z. Simon, *Rev. Roum. Chim.* **10**, 1059 (1965).

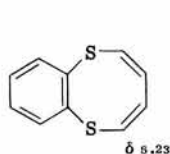
³⁸¹ W. Schroth and B. Werner, *Angew. Chem. Int. Ed. Engl.* **6**, 697 (1967).

³⁸² W. Schroth, F. Billig, and A. Zschunke, *Z. Chem.* **9**, 184 (1969).

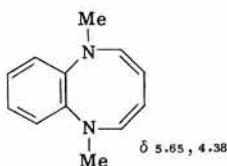
³⁸³ D. L. Coffen, Y. C. Poon, and M. E. Lee, *J. Amer. Chem. Soc.* **93**, 4627 (1971).

³⁸⁴ H.-J. Shue and F. W. Fowler, *Tetrahedron Lett.*, 2437 (1971).

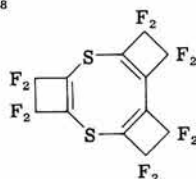
³⁸⁵ M. O. Riley and J. D. Park, *Tetrahedron Lett.*, 2871 (1971).



(161)



(162)

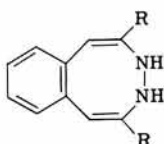


(163)

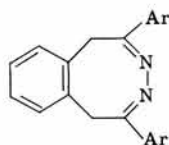
Both Vol'pin³⁷⁷ and Balaban and Simon³⁸⁰ suggested that the isomeric compounds containing the two heteroatoms adjacent to each other have reduced stability (cf. Section III.F, 2, following). The explanation given by Vol'pin, of insufficient molecular orbitals to accommodate the *p*-electrons, has, however, been disputed by the second group. HMO calculations by Allinger and Youngdale³⁸⁶ predicted substantial DE for the nitrogen analogs of this type of compound, **164** and **165** (*R* = H), but the failure of **166** to isomerize to **165** (*R* = Ar) probably illustrates the unreliability of the HMO method for this type of assessment. Paudler and Zeiler,³⁸⁷ however, have claimed that UV data for **167a-c** show conjugation, indicative of some tendency of the central ring to become planar.



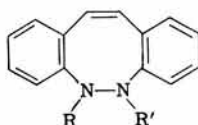
(164)



(165)



(166)



(167a) *R* = *R'* = H

(167b) *R* = H, *R'* = Me

(167c) *R* = *R'* = Me

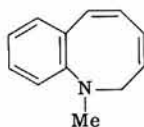
³⁸⁶ N. L. Allinger and G. A. Youngdale, *J. Org. Chem.* **25**, 1509 (1960).

³⁸⁷ W. W. Paudler and A. G. Zeiler, *J. Org. Chem.* **34**, 3237 (1969).

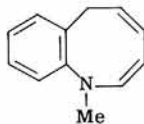
Of all the rings examined only the non-benzo-fused compound **163** apparently has sufficient resonance energy to overcome the strain involved in acquiring planarity. Fusion of an aromatic ring to a benzene nucleus is well known to reduce its aromaticity and this may account in part for the apparent nonplanarity and nonaromaticity of the fused analogs.

2. Anionic Compounds

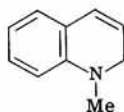
An alternative approach to a ten- π -electron system is the generation of anionic species. Coates and Johnson³⁸⁸ have examined the kinetic acidities of **168** and **169** and compared them with the acidities of **170** and **171**.



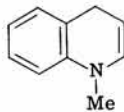
(168)



(169)

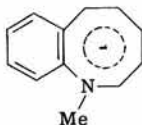


(170)



(171)

They reported that there was only a moderate enhancement in the former and concluded that the anion **172** could only exhibit a small degree of aromatic character. Similar studies on the dibenzo-fused analogs failed to detect any aromatic stabilization of the anions.



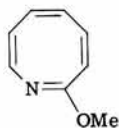
(172)

Paquette *et al.*³⁸⁹ examined a number of derivatives of the nitrogen analog of cyclooctatetraene, e.g., **173**, and like the hydrocarbon these

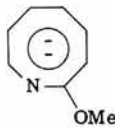
³⁸⁸ R. M. Coates and E. F. Johnson, *J. Amer. Chem. Soc.* **93**, 4016 (1971).

³⁸⁹ L. A. Paquette, J. F. Hansen, and T. Kakihana, *J. Amer. Chem. Soc.* **93**, 168 (1971).

readily form stable dianions **174**. The DE of 5.1β calculated for the azocine dianion is greater than that for the cyclooctatetraene dianion and is evidently more than sufficient to compensate for the ring strain of the planar conformation.



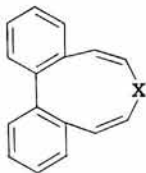
(173)



(174)

G. NINE-MEMBERED HETEROAROMATIC RING COMPOUNDS

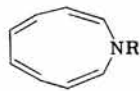
In the past few years a considerable amount of work has been directed towards the study of the heterocyclic analogs of cyclononatetraene—compounds commonly referred to as the heteronins. Apparently the first heteronins to be prepared were the dibenzo-fused analogs **175** ($X = S, O$),³⁹⁰ and subsequently oxonin (**176**),^{391,392} various azonins^{67,393,394} including the



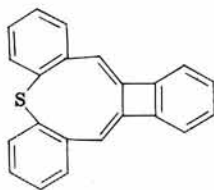
(175)



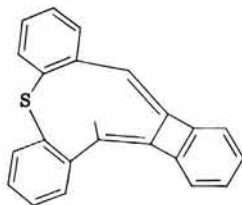
(176)



(177) R = H
(178) R = Me



(179)



(180)

³⁹⁰ A. P. Bindra, J. A. Elix, P. J. Garratt, and R. H. Mitchell, *J. Amer. Chem. Soc.* **90**, 7372 (1968).

³⁹¹ A. G. Anastassiou and R. P. Cellura, *Chem. Commun.*, 903 (1969).

³⁹² S. Masamune, S. Takada, and R. T. Seidner, *J. Amer. Chem. Soc.* **91**, 7769 (1969).

³⁹³ A. G. Anastassiou and J. H. Gebrian, *J. Amer. Chem. Soc.* **91**, 4011 (1969).

³⁹⁴ S. Masamune, K. Hojo, and S. Takada, *Chem. Commun.*, 1204 (1969).

parent **177**,³⁹⁵ and the interesting *cis* and *trans* isomers **179** and **180**³⁹⁶ have been documented.

The compounds may acquire a ten- π -electron system by incorporation of a lone pair from the heteroatom and as such they may be regarded as the ten π -analogs of furan, pyrrole, and thiophene. Anastassiou³⁹⁷ has recently surveyed various properties of heteronins including NMR, UV, and stability data and, in particular, the author points out some marked differences in the properties of **176** and **177**. The former is heat-sensitive, shows UV absorptions similar to the absorptions of cyclononatetraene, and its NMR spectrum (cf. also Masanume *et al.*³⁹²) is typical of a polyenic structure. By contrast **177** is less thermally labile, shows UV absorptions similar to those of cyclononatetraene anion, and the NMR spectrum exhibits peaks centered at δ 7.07, 6.82, and 6.0, some 0.5–0.9 ppm downfield relative to the absorptions in the NMR spectrum of **176**. Further evidence for the aromaticity of **177** and the polyene character of **176** is forthcoming from the *S* values³⁹⁸ (Section II,D, 5). Thus **177** has an *S* value of 1.35, which is greater than the values for benzene (1.0) and for pyrrole (0.9) and is comparable with that of naphthalene (1.35). By contrast the small negative *S* value of -0.07 for **176** is comparable with that of cyclononatetraene (-0.05) and suggests a small degree of antiaromatic character.³⁹⁸

NMR and UV data were also collected for some azonins which show properties intermediate between those of **176** and **177**.⁶⁷ Azonins carrying a carbonyl function at the nitrogen atom tend to be polyenic, presumably because the lone pair is less available for donation into the π -system, while *N*-alkyl- and *N*-benzylazonins more closely resemble **177**. However, the NMR data, UV data, and the low *S* value (0.34) for the *N*-methylazonine (**178**) demonstrate that the aromatic character is less well developed in these compounds than in the parent, and it has been suggested that the rings may be slightly puckered because of unfavorable steric interactions between the substituent on the nitrogen atom and the α -protons.⁶⁷ NMR spectral data for **179** and **180** suggest that these compounds do not sustain ring currents in the nine-membered rings.³⁹⁶ The NMR and UV spectral data of the azonine anion **181** have also been reported recently³⁹⁹ and these were said to demonstrate that the ring is probably planar and aromatic.

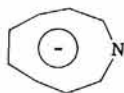
³⁹⁵ A. G. Anastassiou and J. H. Gebrian, *Tetrahedron Lett.*, 825 (1970).

³⁹⁶ P. J. Garratt, A. B. Holmes, F. Sondheimer, and K. P. C. Vollhardt, *J. Amer. Chem. Soc.* **92**, 4492 (1970).

³⁹⁷ A. G. Anastassiou, *Accounts Chem. Res.* **5**, 281 (1972).

³⁹⁸ A. G. Anastassiou and H. Yamamoto, *J. Chem. Soc. D*, 286 (1972).

³⁹⁹ R. T. Seidner and S. Masamune, *J. Chem. Soc. D*, 149 (1972).



(181)

Although data are only available to compare fully the nitrogen- and oxygen-containing compounds, it is interesting that in both the nine- and five-membered ring series the oxygen analog is less aromatic than the nitrogen analog, as is expected on the basis of electronegativity arguments. However, it appears further that oxonin, unlike furan, is fully nonaromatic.

H. BICYCLIC TEN- π -ELECTRON HETEROAROMATIC COMPOUNDS

1. Heteroazulenes

The term "heteroazulenes" is used here rather loosely and certainly unsystematically to describe compounds containing one or more heteroatoms within an azulene-type framework. The aromaticity of heteroazulenes should in principle bear at least some resemblance to that of the six-membered ring heteroaromatics, but this notion has received rather scant attention.

Calculations⁴⁰⁰ have predicted that nitrogen-containing rings, azaazulenes, should show a degree of bond alternation which increases on going from **182** to **183**, and, in that this reflects a reduction in the aromatic character, it is reminiscent of the trend in the azine series (Section III,D, 9). Oxygen- and sulfur-containing structures having potential ten- π -electron systems are of necessity analogs of pyrylium, thiopyrylium, pyranone, and thiapyranone, etc. Zahradník and Párkányi¹⁸⁷ have included in their wide-ranging calculations on sulfur heterocycles, structures **184**, **185** ($R = H$), and **186** and bond orders were estimated for these. Inspection of the results reveals that the bond alternation is least for **184**, and partial support for the view that **184** is the most stable derives from independent determinations of pK_R^+ for **184** and **185** ($R = Me$). The former has a pK_R^+ of 6.0⁴⁰¹ and the latter 2.92⁴⁰² (cf. tropylium 4.7). However, as Turnbo *et al.*⁴⁰¹ point out, the position of equilibrium is dependent upon the stability of both the carbonium ion and its conjugate base. NMR spectra of derivatives of **185**^{70,403} and **184**⁴⁰³ show considerable

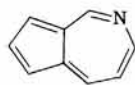
⁴⁰⁰ U. Müller-Westerhoff and K. Hafner, *Tetrahedron Lett.*, 4341 (1967).

⁴⁰¹ R. G. Turnbo, D. L. Sullivan, and R. Pettit, *J. Amer. Chem. Soc.* **86**, 5630 (1964).

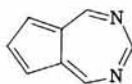
⁴⁰² A. A. Ginesina and A. V. El'tsov, *J. Gen. Chem. USSR* **39**, 2543 (1969).

⁴⁰³ R. Guilard and P. Founari, *Bull. Soc. Chim. Fr.*, 1437 (1971).

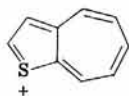
downfield chemical shifts which presumably can be attributed to both ring current effects and the electrophilicity of the rings.



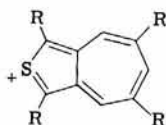
(182)



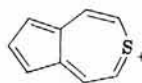
(183)



(184)

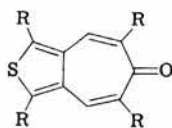


(185)

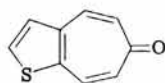


(186)

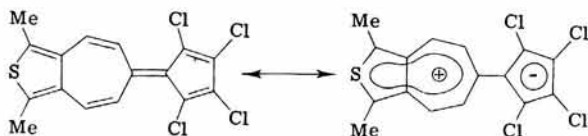
A variety of compounds having the thiaazulenone structures **187** and **188** have been prepared,^{70,403,404} and these include the parent molecules.⁴⁰³ Infrared data, e.g., for **187** (R = Me),⁷⁰ show carbonyl bands at 6.36 and 6.21 μ and the low frequencies imply a degree of single-bond character for the carbonyl function. However, positive solvatochromism observed by Seitz and Mönnighoff⁴⁰⁵ for **189** was interpreted by these authors in terms of a large contribution from the apolar form **189a**, and the lower dipole moments of methyl derivatives of **187** and **188** relative to 4,5-



(187)



(188)



(189a)

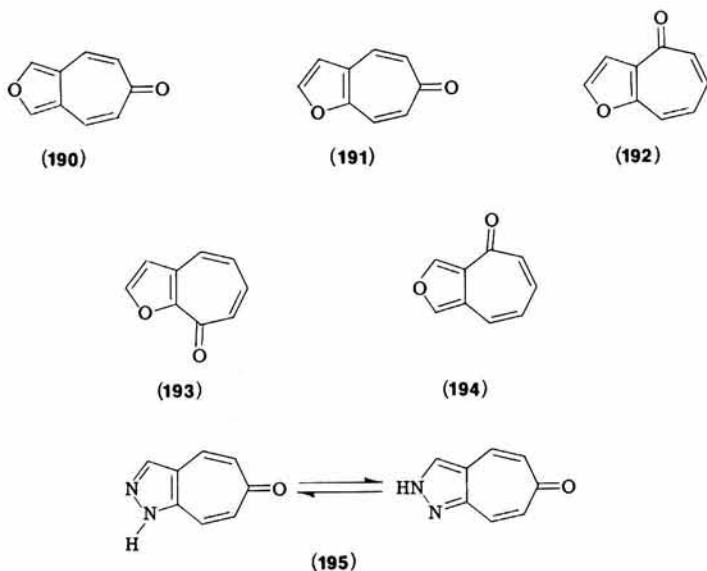
(189b)

⁴⁰⁴ A. V. El'tsov and A. A. Ginesina, *Zh. Org. Khim.* **3**, 191 (1967); A. A. Ginesina and A. V. El'tsov, *ibid.* **4**, 1096 (1968); A. A. Ginesina, L. N. Kivokurtseva, and A. V. El'tsov, *ibid.* **5**, 570 (1969).

⁴⁰⁵ G. Seitz and H. Mönnighoff, *Angew. Chem. Int. Ed. Engl.* **9**, 907 (1970).

benzotropone led Lumbroso *et al.*⁴⁰⁶ to conclude that contributions from $\text{—S}^+=\text{C—C—O}^-$ forms in these compounds are small. Inspection of the NMR data⁴⁰³ for **187** (R = H) and **188** is suggestive of dienone character which is greater in the former, and this would seem to correspond well with the predicted order of aromatic character for the analogous cations **185** and **184**.¹⁸⁷

In the oxygen series, Cook and Forbes⁶⁸ discussed the NMR, IR, and UV spectra of **190** and concluded that the seven-membered ring sustains a small ring current compared with that of tropone and that **190** can hardly be regarded as a ten- π -electron aromatic system, a view consistent with two sets of HMO calculations^{407,408} which predicted considerable bond alternation. Klasinc *et al.*⁴⁰⁸ further predicted that **190** has a lower DE than the isomeric structures **191**, **192**, **193**, and **194** and that each of these is less aromatic than the corresponding benzotropone structures. Greco and Pesce⁴⁰⁹ have recently studied the pyrazolo analog (**195**), which appears to exist as such rather than as a hydroxy compound. PMR resonances occur in the same region as for **190**, and from the UV absorption the authors suggest that **195** may lie intermediate between 4,5-benzotropone and **190** on an aromaticity scale.



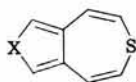
⁴⁰⁶ H. Lumbroso, C. Pigenet, and R. Guillard, *C. R. Acad. Sci. Ser C* **270**, 1905 (1970).

⁴⁰⁷ D. R. Burnham and M. J. Cook, *Tetrahedron Lett.*, 3771 (1968).

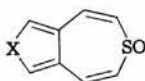
⁴⁰⁸ L. Klasinc, Z. Majerski, and N. Trinajstić, *Z. Phys. Chem.* **239**, 262 (1968).

⁴⁰⁹ C. V. Greco and M. Pesce, *J. Org. Chem.* **37**, 676 (1972).

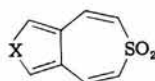
Other systems which should be included in this section are the thiepin derivatives **196** and **197** which, if the analogy with six-membered ring systems is pursued, correspond to dithiin and oxathiin (Section III,D, 11). These compounds, together with the *S*-oxides **198** and **199**, and the *S,S*-dioxides **200** and **201** have been studied by Schlessinger *et al.*^{410,411} UV spectral data have been interpreted in terms of extended conjugation in **196** and **197** relative to the oxidized products, and NMR data were compared with data for the dihydro analogs **202a-c** and **203a-c**. The data show that the chemical shifts of the seven-membered ring protons in the sulfones **200** and **201** are deshielded with respect to the olefinic protons in **202c** and **203c**; whereas the reverse is seen to be true following a similar comparison of the data for the unoxidized compounds **196**, **197**, **202a**, and **203a**. It was suggested⁴¹⁰ during a discussion of the properties of **196** that the structure may have a paramagnetic ring current, from which the authors concluded somewhat curiously that **196** "possesses considerable aromatic-like character" relative to its derivatives **198** and **200**. The X-ray analyses of **196** and **200** were subsequently interpreted⁴¹² as support for this view; the analysis of **196** shows that the molecule is planar with a crystal structure similar to that of azulene (though the crystal disorder precluded measurements of bond lengths). By contrast, the X-ray analysis of **200** revealed that the seven-membered ring is puckered (see Section III,E, 2) and that the carbon-carbon double bonds are very short (1.328–1.336 Å).



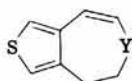
(**196**) X = S
(**197**) X = O



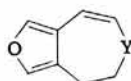
(**198**) X = S
(**199**) X = O



(**200**) X = S
(**201**) X = O



(**202a**) Y = S
(**202b**) Y = SO
(**202c**) Y = SO₂



(**203a**) Y = S
(**203b**) Y = SO
(**203c**) Y = SO₂

⁴¹⁰ R. H. Schlessinger and G. S. Ponticello, *Tetrahedron Lett.*, 3017 (1968).

⁴¹¹ R. H. Schlessinger and G. S. Ponticello, *Tetrahedron Lett.*, 4361 (1969).

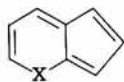
⁴¹² T. D. Sakore, R. H. Schlessinger, and H. M. Sobell, *J. Amer. Chem. Soc.* **91**, 3995 (1969).

Dewar and Trinajstić¹⁰ subsequently calculated the Dewar resonance energy of **196**, neglecting *d*-orbital participation, to be only 3.5 kcal mole⁻¹, substantially lower than the value for thiophene, but reported also that bond lengths showed some divergence from true polyenic bond lengths. They suggested that the earlier interpretation of the X-ray data in terms of the compound's aromaticity is equivocal and that the entropy of the disordered crystal may in itself be sufficient to flatten the ring. They concluded that **196** is best regarded as a thiophene ring fused to a nonaromatic or weakly aromatic moiety.

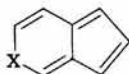
In conclusion, it can be said that the available data do not allow definitive conclusions to be drawn. A number of the compounds are clearly borderline cases; they can neither be regarded as truly "aromatic" nor truly "polyenic". In this respect the heteroazulenes are somewhat comparable to the corresponding six-membered ring structures. Insufficient data are available at the present time to state categorically whether or not a similarity exists between the thienothiepins and dithiin.

2. Pseudoazulenes

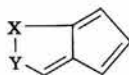
The term "pseudoazulenes" refers to structures in which a heteroatom capable of donating a lone pair of electrons into the conjugated system has formally replaced two *sp*² carbon atoms of the azulene structure; thus the relationship of pseudoazulenes to azulenes is comparable to that of furan, pyrrole, and thiophene to benzene. Alternatively the class may be regarded as bicyclic analogs of the heteronins (Section III.G). Various examples of structures **204–207** are known; structure **208** has also been considered briefly by Zahradník and Párkányi.¹⁸⁷ Indolizine and related structures which may be classified as pseudoazulenes having a bridgehead nitrogen are considered in the following section.



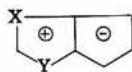
(204)



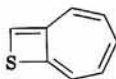
(205)



(206)



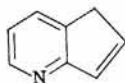
(207)



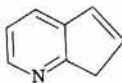
(208)

Pseudoazulenes have attracted theoretical interest, being the subject

of calculations of varying degrees of sophistication. DE's and bond lengths calculated by the HMO method have been used to predict a decreasing order of aromaticity **204** > **205** > **207** > **206**.⁴¹³ Inspection of the bond alternation in **204** (X = S) and **205** (X = S) calculated by Zahradník and Koutecký,⁴¹⁴ again using the HMO method, are in line with this view. Similarly Evleth,⁴¹⁵ using SCF calculations (primarily for a study of electronic spectra, see also Fabian *et al.*⁴¹⁶) showed that **204** (X = NR) is more stabilized than **205** (X = NR), but that both are substantially less aromatic than indole. The author commented that the low resonance energy of **204** (X = NR) is reflected in the fact that the parent **204** (X = NH) exists predominantly in the tautomeric forms **209** and **210**.⁴¹⁷ Borsdorf,^{418, 419} using the HMO method, calculated that the oxygen analog **204** (X = O), DE = 2.66β , is less aromatic than the nitrogen analog **204** (X = NH), DE = 2.79β , and that both values of DE are less than that of azulene, 3.36β . Similar comparisons were made for benzo-fused analogs of these pseudoazulenes.^{419, 420}



(209)



(210)

Raimondi and Favini⁴²¹ calculated bond distances for various pseudoazulenes containing both a pyrrole-type nitrogen and a pyridine-type nitrogen, and their results predict only very minor perturbations of carbon-carbon bond lengths in **204** (X = NR) and **205** (X = NR) on replacing a =CH— moiety by =N—.

NMR spectral data for **205** (X = NPh)⁴²² and **205** (X = S)^{422, 423} show absorptions in the region δ 6.6–8.4, but methyl substitution at either the C-1 or C-4 position of the latter system leads to an upfield shift of the C-3 proton to $\delta \sim 6$ ppm. The NMR spectrum of **211** shows a peak for

⁴¹³ G. V. Boyd, *Tetrahedron Lett.*, 1421 (1965).

⁴¹⁴ R. Zahradník and J. Koutecký, *Collect. Czech. Chem. Commun.* **28**, 1117 (1963).

⁴¹⁵ E. M. Evleth, *Theor. Chim. Acta* **16**, 22 (1970).

⁴¹⁶ J. Fabian, A. Mehlhorn, and R. Zahradník, *Theor. Chim. Acta* **12**, 247 (1968).

⁴¹⁷ A. G. Anderson and H. L. Ammon, *Tetrahedron* **23**, 3601 (1967).

⁴¹⁸ R. Borsdorf, *Z. Chem.* **4**, 422 (1964).

⁴¹⁹ R. Borsdorf, *J. Prakt. Chem.* **32**, 211 (1966).

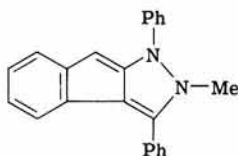
⁴²⁰ R. Borsdorf, *Z. Chem.* **5**, 187 (1965).

⁴²¹ M. Raimondi and G. Favini, *Gazz. Chim. Ital.* **98**, 433 (1968).

⁴²² A. G. Anderson, W. F. Harrison, and R. G. Anderson, *J. Amer. Chem. Soc.* **85**, 3448 (1963).

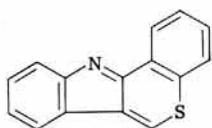
⁴²³ R. Radeaglia and R. Wagner, *Z. Chem.* **4**, 145 (1964).

the pseudoazulene ring proton at 5.74 ppm, which argues against substantial aromatic character in this system.⁴²⁴

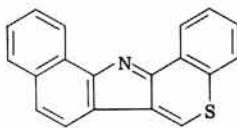


(211)

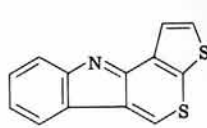
The mass spectra of various benzo-fused pseudoazulenes e.g., **212**, **213**, and **214** show the mass ion as the base peak, and the authors⁴²⁵ have associated this with the aromaticity of these structures. However, it must be said that the overall picture is somewhat unclear at the present time.



(212)



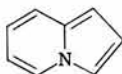
(213)



(214)

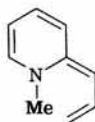
3. Indolizine and Some Related Compounds

Dewar and Trinajstić¹³ calculated the Dewar resonance energy of indolizine (**215**) to be 6.9 kcal mole⁻¹, and the structure may perhaps be



(215)

best regarded as a derivative of pyrrole (5.6 kcal mole⁻¹). Such a view is consistent with the SCF-CI calculations by Evleth⁴¹⁵ which showed that the DE of **215** and of isoindole are comparable and less than the DE of indole. Basicity measurements show that the ERE of the five-membered ring is substantial.²⁷³ [In this approach the basicity of **215** (pK_a 3.94) is



(216)

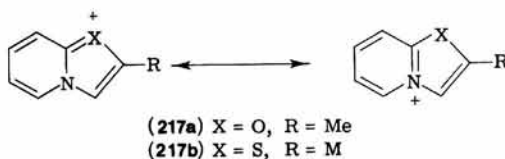
⁴²⁴ G. V. Boyd and D. Hewson, *J. Chem. Soc., C* 2959 (1968).

⁴²⁵ N. P. Buu-Hoi, A. Croisy, P. Jacquignon, A. Martani, and A. Ricci, *J. Heterocycl. Chem.* **7**, 931 (1970).

compared with that of **216** (estimated pK_a 18.3). The difference in resonance energy of the two bases is then calculated to be 24 kcal mole⁻¹.] LCAO-SCF-MO calculations⁴²⁶ predicted substantial bond alternation in **215**; however, this was not reproduced by the SCF-CI calculations of Galasso *et al.*⁴²⁷

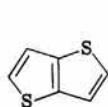
Earlier, Mason²⁵⁶ studied the aza analogs of indolizine and indole and found that the electronic spectra of the former series conformed more closely to the spectrum of the indenyl anion, from which it was concluded that π -electron delocalization is more pronounced in this series, a result which appears to be contrary to the conclusions from MO calculations. Proton resonances in the PMR spectrum of **215** and of various aza-indolizines^{428, 429} show that these compounds sustain a ring current, and Black, Brown, and Heffernan,⁴²⁹ in a study designed to correlate electron density and chemical shift data, commented that the data also support Mason's view that π -electron delocalization is more extensive in these compounds than in the indole series.

Oxa⁴³⁰ and thia⁴³¹ derivatives of indolizine, e.g., **217a** and **217b**, also show substantial deshielding of the ring protons, although here the positive charge on the ring is itself a deshielding factor. Compound **217a** shows no ring protons resonances at a higher field than δ 7.8, and **217b** shows no peaks at higher field than δ 7.5.

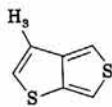


4. Thienothiophenes (Thiophthenes)

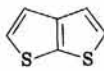
There are four possible isomeric thiophthenes, **218**, **219**, **220**, and **221** and examples of each have been reported. The fourth structure can be



(218)



(219)



(220)



(221)

⁴²⁶ C. Aussems, S. Jaspers, G. Leroy, and F. Van Remoortere, *Bull. Soc. Chim. Belg.* **78**, 479 (1969).

⁴²⁷ V. Galasso, G. De Alti, and A. Bigotto, *Theor. Chim. Acta* **9**, 222 (1968).

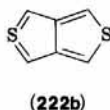
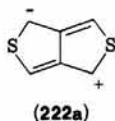
⁴²⁸ W. W. Paudler and J. E. Kuder, *J. Heterocycl. Chem.* **3**, 33 (1966).

⁴²⁹ P. J. Black, R. D. Brown, and M. L. Heffernan, *Aust. J. Chem.* **20**, 1305, 1325 (1967).

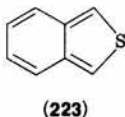
⁴³⁰ C. K. Bradsher and M. F. Zinn, *J. Heterocycl. Chem.* **1**, 219 (1964); **4**, 66 (1967).

⁴³¹ C. K. Bradsher and D. F. Lohr, *J. Heterocycl. Chem.* **3**, 27 (1966).

represented as a resonance hybrid of mesoionic canonical forms, e.g., **222a**, and/or forms in which *d*-orbital participation is invoked, e.g., **222b**. (For discussions of *d*-orbital participation see, for example, Dewar and Trinajstić¹⁰ and Salmond.³⁰⁸)



The X-ray structural determination of thieno[3,2-*b*]thiophene (**218**) has been reported: the central bond is of comparable length to the other bonds $\alpha\beta$ to the sulfur atoms,⁴³² and the data suggest that there is considerable aromatic character. Using SCF-MO calculations on a *p* model, Clark⁴³³ calculated that structure **218** is 46 kcal mole⁻¹ more stable than **221**. More recently Dewar and Trinajstić¹⁰ calculated the Dewar resonance energy, ignoring *d*-orbitals, for the series **218**–**221** and obtained the values 11.3, 5.9, 10.5, and –33.9 kcal mole⁻¹, respectively. The ratios of the resonance energies of both **218** and **220** to that of thiophene are comparable with the ratio of the resonance energies of naphthalene to benzene. By contrast thieno[3,4-*b*]thiophene (**219**) has lower Dewar resonance energy than thiophene, 6.5 kcal mole⁻¹, and compares somewhat with **223**.



Proton chemical shift data^{434,435} for **218**, **219**, and **220** or simple derivatives of these are consistent with the conclusions to be drawn from the Dewar resonance energy calculations. Thus proton 3 in **219**⁴³⁴ absorbs at δ 6.70–6.79, which is at higher field than the proton absorptions reported for the other structures.

The initial report⁴³⁶ that **224** was observed as an unstable intermediate has been considered^{10,433} to be consistent with the predictions of instability drawn from the MO calculations. However, the subsequent preparation of the stable compound **225**,⁴³⁷ which shows the mass ion as the base

⁴³² E. G. Cox, R. J. J. H. Gillot, and G. A. Jeffrey, *Acta Crystallogr.* **2**, 356 (1949).

⁴³³ D. T. Clark, *Tetrahedron Lett.*, 5257 (1967).

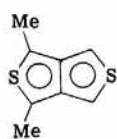
⁴³⁴ H. Wynberg and D. J. Zwanenburg, *Tetrahedron Lett.*, 761 (1967).

⁴³⁵ V. P. Litvinov and G. Fraenkel, *Izv. Akad. Nauk. SSSR Ser. Khim.*, 1828 (1968).

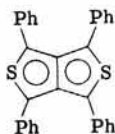
⁴³⁶ M. P. Cava and N. M. Pollack, *J. Amer. Chem. Soc.* **89**, 3639 (1967).

⁴³⁷ M. P. Cava and G. E. M. Husbands, *J. Amer. Chem. Soc.* **91**, 3952 (1969).

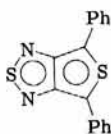
peak in the mass spectrum, as well as the preparations of compounds such as **226**⁴³⁸ and **227**⁴³⁹ seem contrary to these predictions and imply a deficiency in the assumption of a simple *p*-orbital model.



(224)



(225)



(226)

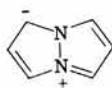


(227)

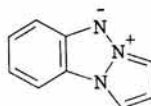
The four isomers have been subject to a number of calculations designed to predict or account for preferred sites of reactivity, UV spectral data, and bond lengths, but the results have not been interpreted in terms of aromatic character (for the more recent calculations see Clark *et al.*⁴⁴⁰).

5. Miscellaneous Heteropentalenes

The NMR spectra of the chemically unstable diazapentalene (**228**) and the benzo derivative of the triazapentalene (**229**) have been studied. The former shows absorptions at δ 6.65 and 7.01⁴⁴¹ (cf. Solomons and Voigt^{102, 442}), and the latter shows⁴⁴³ one proton at δ 6.66 with the remainder in a broad envelope at 6.92–7.60 ppm.



(228)



(229)

Studies on the tetraazapentalenes have been rather more extensive. The crystal structures of **230a** and **230b** show⁴⁴⁴ that the system is planar

⁴³⁸ J. D. Bower and R. H. Schessinger, *J. Amer. Chem. Soc.* **91**, 6891 (1961).

⁴³⁹ M. Carmack, R. W. Street, and R. V. Wen, *Nat. Meeting Amer. Chem. Soc.*, 158th, 1969.

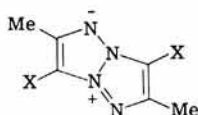
⁴⁴⁰ D. T. Clark, *Tetrahedron Lett.*, 2889 (1967); N. Trinajstić and Z. Majerski, *Z. Naturforsch. A* **22**, 1475 (1967); N. Trinajstić and A. Hinchliffe, *Croat. Chem. Acta* **39**, 119 (1967); D. T. Clark, *Tetrahedron* **24**, 2567 (1968); *J. Mol. Spectrosc.* **26**, 181 (1968); J. Fabian, A. Mehlhorn, and R. Zahradník, *J. Phys. Chem.* **72**, 3975 (1968); A. Skancke and P. N. Skancke, *Acta Chem. Scand.* **24**, 23 (1970); A. Tajiri, T. Asona, and T. Nakajima, *Tetrahedron Lett.*, 1785 (1971).

⁴⁴¹ S. Trofimenko, *J. Amer. Chem. Soc.* **87**, 4393 (1965).

⁴⁴² T. W. G. Solomons and C. F. Voigt, *J. Amer. Chem. Soc.* **87**, 5256 (1965).

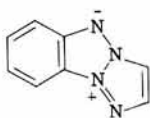
⁴⁴³ B. M. Lynch and Y.-Y. Hung, *J. Heterocycl. Chem.* **2**, 218 (1965).

⁴⁴⁴ M. Brufani, W. Fedeli, G. Giacomello, and A. Vacic, *Chem. Ber.* **96**, 1840 (1963).

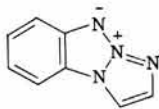
(230a) X = CO₂Rb

(230b) X = Br

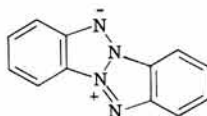
and can be regarded as aromatic. The aromaticity of the benzo and dibenzo tetraazapentalene series (231), (232), (233), (234) has been the subject of a study by researchers from the E. I. du Pont de Nemours Company^{445,446} (see also Carboni *et al.*⁴⁴⁷); heats of combustion were measured for each compound and the data were used to derive ERE values. The choice of suitable nonaromatic models is not straightforward for such systems but the results nevertheless demonstrated substantial aromaticity for the tetraazapentalene nuclei. Values of 84.7, 92.8, 121.7, and 132.4 kcal mole⁻¹ were reported for the ERE of 231 to 234, respectively; the latter two values surpass the values of 110 and 116.5 kcal mole⁻¹ for the carbocyclic systems naphthacene and chrysene. HMO calculations were reported⁴⁴⁵ which were in accord with the greater aromaticity of the isomers with the branched nitrogen chain over those with the Z-shaped chain. The NMR spectra of both 233⁴⁴⁸ and 234⁴⁴⁹ have been examined in



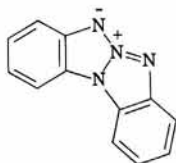
(231)



(232)



(233)



(234)

⁴⁴⁵ Y. T. Chia and H. E. Simmons, *J. Amer. Chem. Soc.* **89**, 2638 (1967).

⁴⁴⁶ R. A. Carboni, J. C. Kauer, J. E. Castle, and H. E. Simmons, *J. Amer. Chem. Soc.* **89**, 2618 (1967).

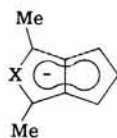
⁴⁴⁷ R. A. Carboni and J. E. Castle, *J. Amer. Chem. Soc.* **84**, 2453 (1963); R. A. Carboni, J. C. Kauer, W. R. Hatchard, and R. J. Harder, *ibid.* **89**, 2627 (1967); J. C. Kauer and R. A. Carboni, *ibid.* **89**, 2633 (1967); R. J. Harder, R. A. Carboni, and J. E. Castle, *ibid.* **89**, 2643 (1967).

⁴⁴⁸ J. H. Hall, J. G. Stephanie, and D. K. Nordstrom, *J. Org. Chem.* **33**, 2951 (1968).

⁴⁴⁹ J. H. Hall, *J. Org. Chem.* **36**, 217 (1971).

detail and there is a reasonable correlation between chemical shift and charge density as calculated by the HMO method.⁴⁴⁵ A theoretical study of the electronic structure of the parent of ring system **230** has also been reported.⁴⁵⁰

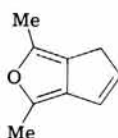
The NMR spectral data for anionic heteropentalenes show that the species are truly ionic, rather than covalently bonded (to the metal counterion). Proton chemical shifts for the series **235a**,¹⁰⁹ **235b**,¹¹⁰ and **235c**¹⁰⁸ demonstrate that the species are symmetrical and that the negative charge is delocalized over the ring. Cantrell and Harrison¹¹⁰ commented that the methyl shift in the oxygen analog is shifted upfield relative to the methyl shifts in the olefin precursor **236** from which **235b** was derived, whereas there is no such shift in the sulfur series. This, they suggested, could be due to either a greater negative charge on the hetero ring of **235b** relative to that on **235a**, or, alternatively, that the former sustains a weaker ring current.



(235a) X = S

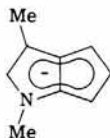
(235b) X = O

(235c) X = NMe

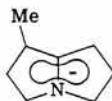


(236)

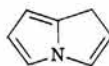
1-Azapentalenyl anions,⁴⁵¹ e.g., **237** and the 4-azapentalenyl anion **238**,⁴⁷ also show signals in the NMR spectrum consistent with extensive delocalization of the negative charge. The latter further exhibits a UV spectrum very similar to that of pentalenyl dianion. An attempt was made to relate the estimated pK_a , 29, of 3H-pyrrolizine (**239**) with the difference in HMO delocalization energies of the π -electrons in the anion and neutral compounds, but with only a limited degree of success.⁴⁷



(237)



(238)



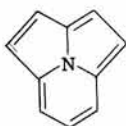
(239)

⁴⁵⁰ L. Paoloni, P. Gramaccioni, and A. Vaciago, *Theor. Chim. Acta* **5**, 102 (1966).

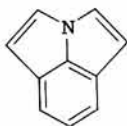
⁴⁵¹ H. Volz, U. Zirngibl, and B. Messner, *Tetrahedron Lett.*, 3593 (1970); H. Volz and R. Draese, *ibid.*, 4917 (1970).

I. POLYCONDENSED HETEROAROMATIC COMPOUNDS

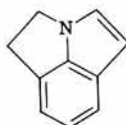
HMO calculations on cycl[3.2.2]azine (**240**)^{25,26} attributed substantial DE to the molecule and more recently Dewar and Trinajstić⁴⁵² calculated a value for the Dewar resonance energy of 18.9 kcal mole⁻¹. The aromaticity of **240** is reflected in the PMR spectrum¹⁰¹ which shows proton resonances in the region 7.20 to 7.86 ppm. Paudler and Shin⁴⁵³ examined an isomer of **240**, viz., pyrrolo[3,2,1-*h*,*i*]indole (**241**), and from a comparison of the benzene-induced shifts of the proton resonances in both **241** and 7-methylindole suggested that there is no loss of aromaticity in **241** relative to the indole derivative. A further comparison of the proton chemical shifts in **241** and its dihydro derivative **242** led the authors to suggest that the former is the more aromatic.



(240)



(241)



(242)

By contrast to **240**, which contains 10 peripheral π -electrons, cycl[3.3.3]azine (**243**), which has 12, might be anticipated to lack aromatic character. Early HMO calculations, however, predicted^{25,26} a greater DE for **243** than for **240**, but the recent preparation and investigation of **243** by Farquhar and Leaver⁴⁵⁴ demonstrated the inaccuracy of this prediction, and subsequently Dewar and Trinajstić reported⁴⁵² a negative value for the Dewar resonance energy. The PMR resonances reported by Farquhar and Leaver⁴⁵⁴ are shown in diagram **243** and the high field shifts provide good evidence that the compound sustains a paramagnetic ring current.

Studies on derivatives of heterophenalenenes where the heteroatoms are part of the peripheral skeleton⁴⁵⁵⁻⁴⁵⁸ lead to the conclusion that such compounds have little aromatic character in the hetero rings. Thus the protons at C-2 and C-3 of **244** absorb at δ 5.63 and 6.03, respectively,⁴⁵⁶

⁴⁵² M. J. S. Dewar and N. Trinajstić, *J. Chem. Soc. A*, 1754 (1969).

⁴⁵³ W. W. Paudler and H. G. Shin, *J. Heterocycl. Chem.*, **6**, 415 (1969).

⁴⁵⁴ D. Farquhar and D. Leaver, *Chem. Commun.*, 24 (1969).

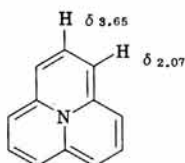
⁴⁵⁵ S. O'Brien and D. C. C. Smith, *J. Chem. Soc.*, 2907 (1963).

⁴⁵⁶ P. Flowerday and M. J. Perkins, *J. Chem. Soc. C*, 298 (1970).

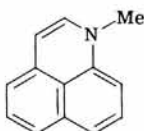
⁴⁵⁷ P. H. Lacy and D. C. C. Smith, *J. Chem. Soc. C*, 747 (1971).

⁴⁵⁸ A. F. Pozharskii and E. N. Malysheva, *Khim. Geterotsikl. Soedin.*, 103 (1970).

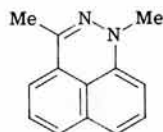
and shifts observed for various $1H$ 1,2-diazaphenalenenes, e.g., **245**, have been interpreted⁴⁵⁷ in terms of a negligible ring current in the heterocyclic ring. By contrast, the tetracyclic ring compound **246**, which shows NMR signals for the ring protons of the heterocyclic ring at δ 6.8 and 8.2, clearly sustains a substantial diamagnetic ring current which can be associated with the 14 peripheral π -electrons.⁴⁵⁶ A similar interpretation can be drawn for **247–250** from the observations⁴⁵⁹ that the proton signals in these



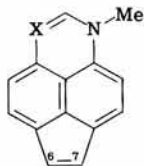
(243)



(244)

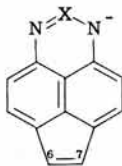
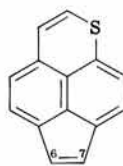


(245)



(246) X = CH

(247) X = N

(248) X = S⁺(249) X = NMe⁺

(250)

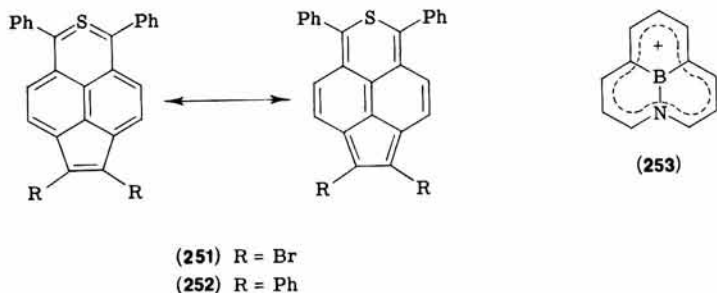
structures are deshielded relative to the resonances in their 6,7-dihydro analogs. The sulfur heterocycles **251** and **252**,^{460, 461} may provide an example of a compound having a tetracoordinated sulfur, but it has been pointed out⁴⁵⁹ that the large value of $J_{4,5}$ (9.0 Hz) in **251** may be indicative of a large contribution from the quinonoid-type structure **251b**. Finally, Dewar and Jones⁴⁶² reported the NMR spectrum of the 12,11-borazaphenalenium cation **253**, a structure isoelectronic with the phenalenium cation, and which exhibits absorptions in the aromatic region at δ 6.6–7.4.

⁴⁵⁹ P. Flowerday, M. J. Perkins, and A. R. J. Arthur, *J. Chem. Soc. C*, 290 (1970).

⁴⁶⁰ I. S. Ponticello and R. H. Schlessinger, *J. Amer. Chem. Soc.* **90**, 4190 (1968).

⁴⁶¹ J. M. Hoffmann and R. H. Schlessinger, *J. Amer. Chem. Soc.* **91**, 3953 (1969).

⁴⁶² M. J. S. Dewar and R. Jones, *Tetrahedron Lett.*, 2707 (1968).



J. GENERAL CONCLUSION

Overall very little quantitative evidence is available regarding the aromaticity of heterocycles. This applies particularly to ring systems other than five- or six-membered. Thus three- or four-membered rings which could possess considerable aromaticity are often unknown or of doubtful existence, and the situation is little better for seven-membered rings and, on the whole, worse for larger-membered rings.

Among monocyclic five-membered rings, the aromaticity of furan, thiophene, and pyrrole has been extensively investigated, but that of other five-membered rings, and especially azoles with several heteroatoms, very much less. Again of monocyclic six-membered rings, pyridine has been quite extensively investigated, the azines less so, and rings containing heteroatoms other than nitrogen very little. A large number of bicyclic and polycyclic compounds containing further five-, six-, and/or seven-membered rings are known; little is known of their quantitative aromaticity.

The authors of this review believe that the rationalization of the reactions of heterocyclic compounds would be considerably assisted by semiquantitative estimates of aromaticity; clearly this field is wide open for development. The existing information needs to be collated and extended and new quantitative investigations are required. More work is needed on the interrelationship of the various available methods, existing methods need to be generalized, new general methods discovered, and the general relation of aromaticity to reactivity developed.

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